Nomacopan
Treatment of COVID-19 Pneumonia

September 1, 2020

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Discussion Outline

- Akari introduction
- Nomacopan dual mode of action in both C5 and LTB4
- Nomacopan treatment for COVID-19 pneumonia
- Evidence supporting nomacopan as potential COVID-19 pneumonia treatment
- Nomacopan clinical studies, underway and planned, related to COVID-19 pneumonia

Nomacopan: in clinical studies for COVID-19 pneumonia

- Strong rationale for role of C5 and LTB4 in treating multiple pathways involved COVID-19-driven pneumonia
- Nomacopan has two separate independent binding sites for C5 and LTB4
- Differentiated from competing treatments by inhibition of multiple inflammatory pathways
- Multiple integrated clinical programs
  - US : Expanded access program moving to proposed randomized study
  - Brazil : Recruitment to proof of principle study completed;
    Following DMSB plan to move to randomized study
  - UK : Collaborating with AGILE platform* and analyzing observational study data
- Broad acting nature of nomacopan has potential applicability across range of lung conditions
- Safety and clinical potential of nomacopan underpinned by broader Phase 3 clinical program

* AGILE-: Accelerating COVID-19 dRug Development - Phase 1/2 trial platform/ AGILE is a novel clinical trial platform seeking additional COVID-19 therapies. AGILE is led by the University of Liverpool, with support from the Liverpool School of Tropical Medicine, Southampton Clinical Trials Unit and Lancaster University

COVID-19 program builds on nomacopan data from clinical testing in multiple preceding indications

Category	Disease	Preclinical	Phase 1	Phase 2	Phase 3
Pulmonary	COVID-19 pneumonia				
Dermatology	Bullous Pemphigoid				
Hematology	Thrombotic Microangiopathy				
	Paroxysmal Nocturnal Hemoglobinuria *				
Ophthalmology	Atopic Kerato-conjunctivitis				
Other	Back of the eye				

Role of nomacopan in treating COVID-19 pneumonia

Reduce hospital stay, assisted ventilation and mortality by reducing severe inflammatory responses in COVID-19 pneumonia patients

Anti-inflammatory treatment: nomacopan

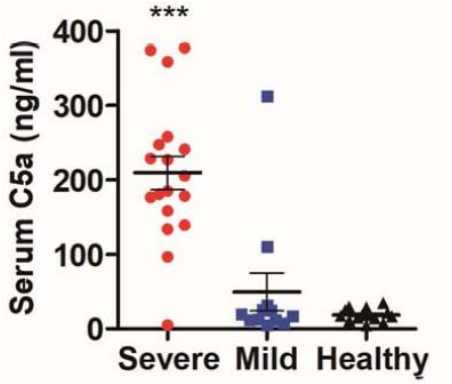
- Circa 5-10% of patients develop respiratory failure
- Inflammation caused by a dysregulated and overly vigorous immune response to COVID
  - Increased levels of neutrophils and production of cytokines (cytokine storm)
  - Tissue damage further amplifies inflammatory responses
- Treatment to inhibit parts of immune system directly involved with this inflammation, central to which are the complement (C5) and leukotriene (LTB4) pathways - both critical parts of this over-active innate immune response

Scientific understanding of COVID-19 pneumonia has developed rapidly since the pandemic began

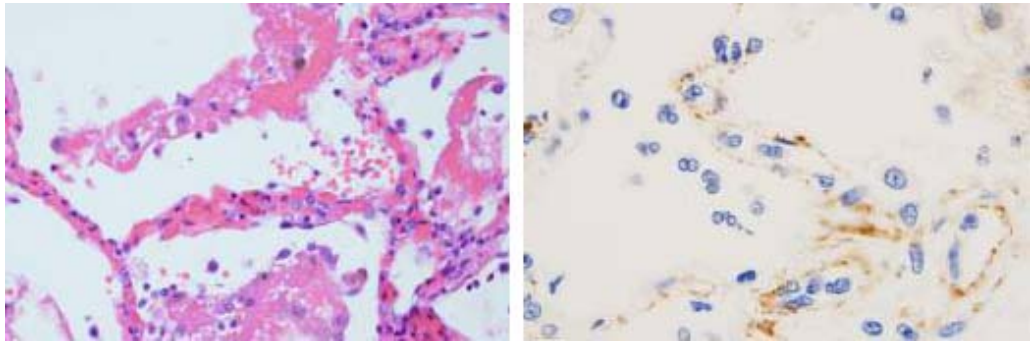
1. Initial focus on ARDS / cytokine storms
2. Vascular damage observed in autopsies of COVID-19 pneumonia patients
3. Elevated complement C5b9 and C5a reported in severe patients
4. Two step disease progression
5. Long term organ damage increasingly observed
6. Initial data on anti-inflammatories (IL-6, dexamethasone etc) mixed – still an urgent need for an effective treatment for hospitalised patients

Pulmonary endothelial injury associated with dysregulation of complement

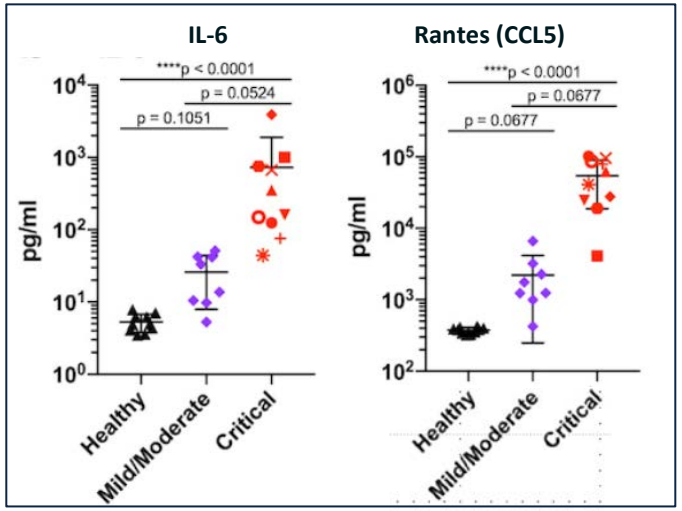
Gao et al sC5a levels in severe & mild SARS-CoV-2 pneumonia



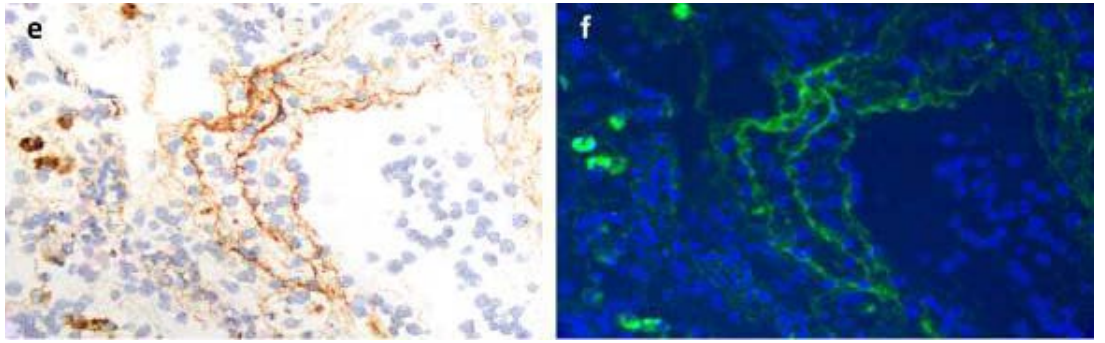
SARS-CoV-2 pneumonia with Thrombotic Microangiopathy (TMA) with **C5a**



Patterson et al IL-6 and Rantes levels in severe COVID



Terminal complement effector **C5b-9** in the alveolar septa in SARS-coV-2 pneumonia



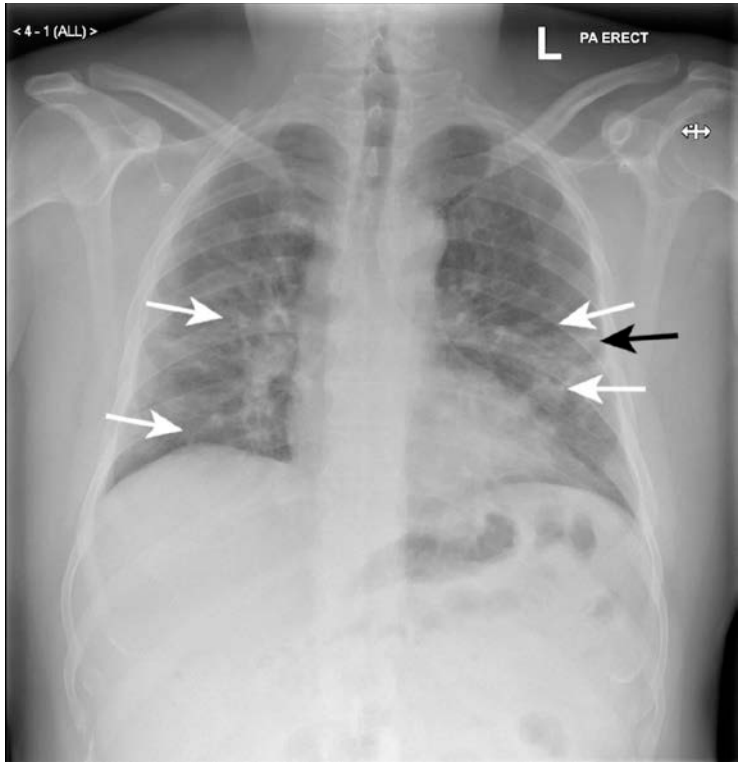
A clear association between Complement activation and COVID-19 pneumonia

Two step process to severe lung illness in COVID-19

Development of severe respiratory illness

- Many patients with acute COVID-19 have symptoms involving their respiratory systems, characterized by dry cough, dyspnoea, hypoxaemia, and abnormal imaging results
- Although most patients had mild-to-moderate disease, 5–10% progress to severe or critical disease, including pneumonia and acute respiratory failure
- Severe cases describe a two-step disease progression, starting with a mild-to-moderate presentation, followed by a **secondary respiratory worsening 9–12 days** after the first symptom onset
- Respiratory deterioration is concomitant with extension of ground-glass lung opacities on chest CT scans, lymphocytopenia, and **high prothrombin time** and **D-dimer levels**

Ground glass and streaking shadows



Source: UK Faculty of Pharmaceutical Medicine

COVID 19 pathology: Leukotriene and complement pathways

Leukotriene and complement are both key pathways in innate immune response and are believed to be strongly implicated in driving inflammation in COVID pneumonia

Leukotriene

- Neutrophil accumulation (and associated NETs) in lungs is a key feature of COVID-pneumonia, resulting in cytokine storm and associated epithelial damage in the lung
- LTB4 is one of the most potent chemo attractants of neutrophils* and elevated levels of leukotrienes in the lung are associated with ARDS
- Inhibition of leukotriene pathway is proven as a treatment for inflammation in lung

Complement

- Levels of both C5a and C5b9 (by-products of C5 whose cleavage is inhibited by nomacopan) are correlated with COVID-19 pneumonia disease severity
- Complement activation associated with abnormal coagulation with both pulmonary and cutaneous thrombotic microangiopathy and related end organ damage

Nomacopan has two separate independent binding sites and inhibits both the leukotriene and complement pathways

* Funk CD and Ardakani A (2020)

Two primary pathways driving COVID-19 pneumonia

Nomacopan inhibits key COVID-19 pneumonia inflammatory pathways

COVID 19 believed to trigger multiple inflammatory pathways

Nomacopan Inhibition

Complement (sC5b9 and C5a)
sC5b9 accrues in lung vascular tissue, C5a promotes thrombosis

↓

Lung vascular damage and microthrombi lowered platelets and increased D-dimer

↓

Dramatic reduction in lung perfusion, respiratory distress, microthrombi in lung and other tissues

LTB4 and C5a
drive neutrophil trafficking and cytokine storm in the lung

↓

Lung epithelial damage raised neutrophils and cytokines

↓

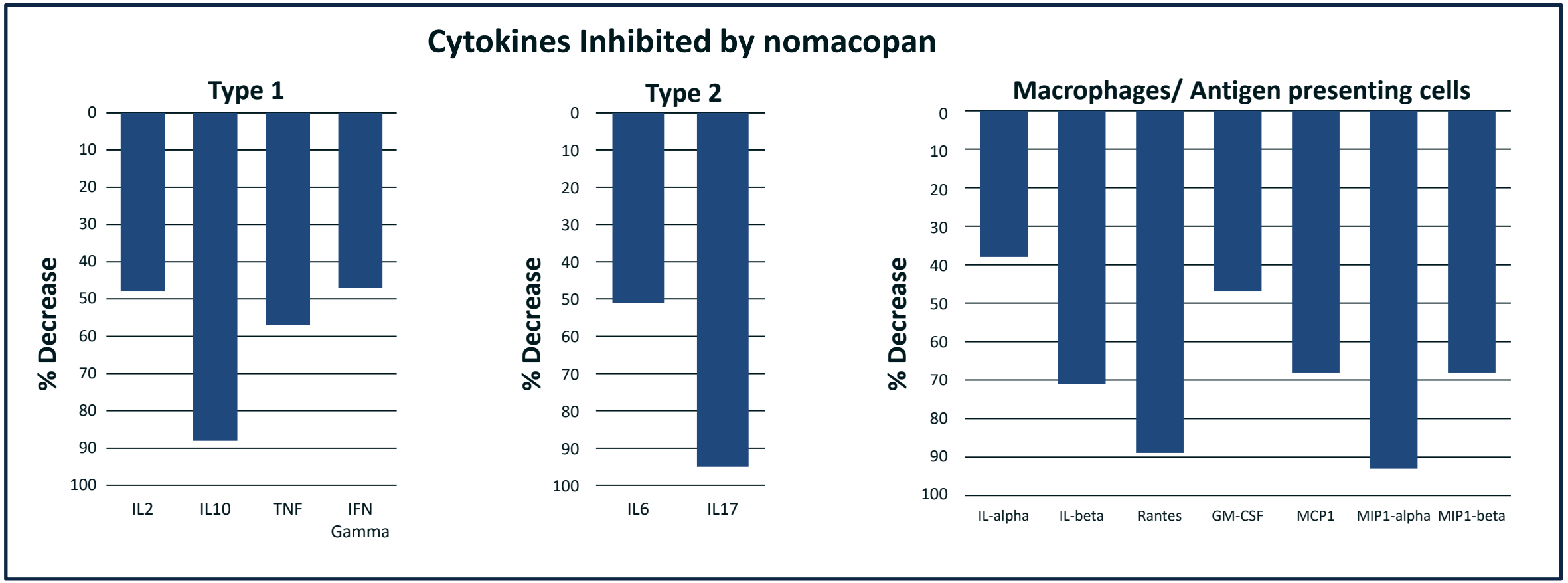
Acute Respiratory Distress

↓

Oxygen support, ventilation, multi organ damage

Nomacopan inhibits downstream cytokine & chemokine signaling cascades implicated in COVID pathology

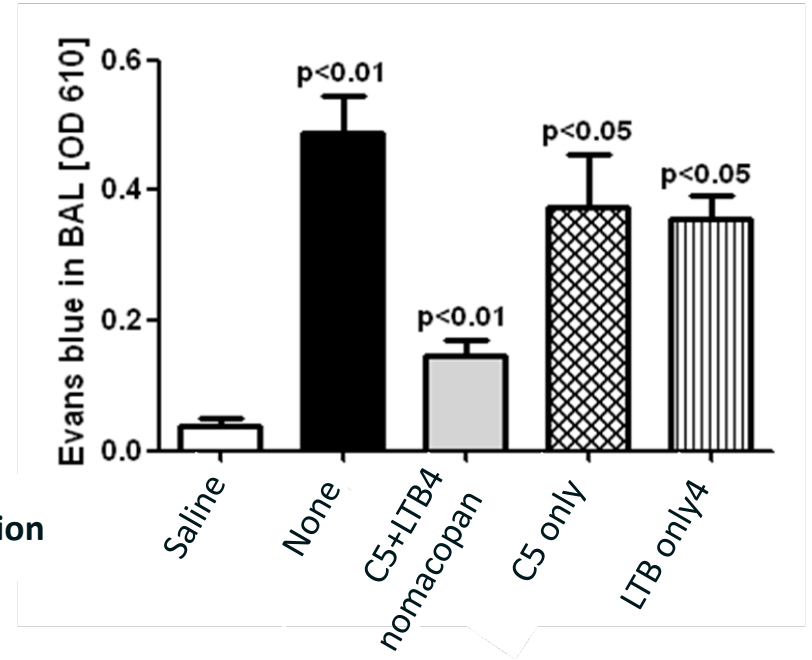
Inflammatory markers inhibited by nomacopan in polymicrobial sepsis mouse model



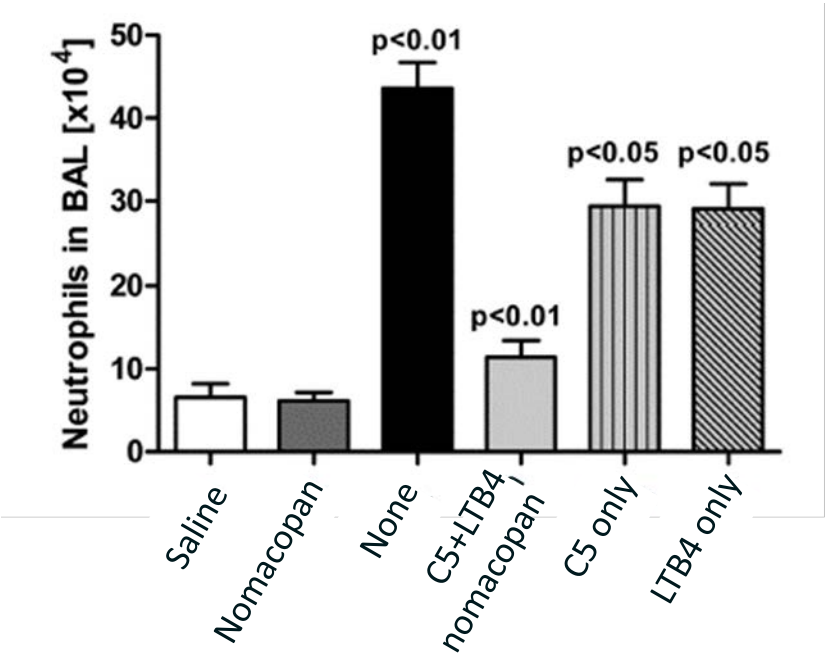
Source: Nomacopan (coversin) data adapted from Figs. 1, 2 & 3 of Huber-Lang et al. J Immunol 2014; 192:5324 – 5331 ;
COVID activity taken from : Mehta P et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet, March 16 2020; 395(10229): 1033 – 1034

Nomacopan's dual inhibition of C5 & LTB4 inhibition more effective than inhibiting C5 or LTB4 alone

Lung model of immune-complex alveolitis
Dual inhibition superior to C5 or LTB4 inhibition alone



Inhibition



- Two forms of Nomacopan one inhibiting C5+LTB4, the other inhibiting C5 only (pre-saturated with LTB4)
- LTB4 only is MK886 a leukotriene inhibitor that inhibits 5-lipoxygenase activator protein (FLAP)
- Source : Roversi et al 2013

Clinical treatment guidelines based on growing understanding of COVID-19 pneumonia

Multiple Pathways	• Anticipated need to inhibit multiple pathways • Complement and cytokines play an important role	Nomacopan inhibits complement and leukotriene pathways
Patient Segmentation	• Timing critical: disease changes dramatically by time on ventilator • Heterogenous patients – biomarker helpful to focus treatment • Need to get patients off treatment quickly once improved, long term immunosuppressant use clinically undesirable	Nomacopan rapid on/off inhibition of C5 and LTB4
Standard of Care Treatment	• SOC changed – dexamethasone and remdesivir improve outcomes in specific patient groups • Long term monitoring important; widespread organ damage	Nomacopan has potential to be additive to SOC
Clinical Trials	• Clinical trials need to be randomized, clinically relevant and with latest SOC	Primary end point normalization of oxygen

Different approaches to inhibiting inflammatory pathways

In trials for COVID pneumonia

Cytokine specific	Complement pathway	Leukotriene pathway	Broad range	Other immune modulators
IL-6 inhibitors GM-CSF inhibitors IFN Gamma inhibitors	C5 inhibitors C5a inhibitors	Montelukast	Dexamethasone	JAK inhibitors BTK inhibitors

Nomacopan inhibits multiple pathways

Standard of care

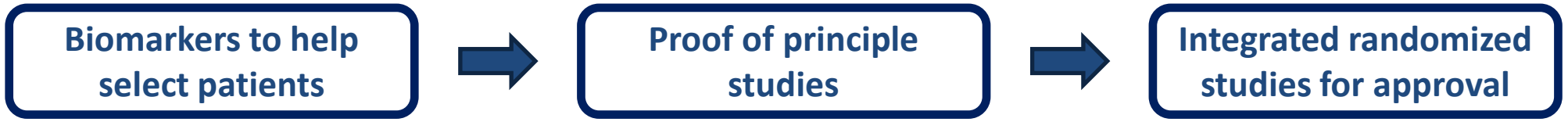
- **Nomacopan blocks multiple cytokines through inhibiting the complement and leukotriene pathways; thrombosis increasingly linked to amplified complement activity (both C5a and C5b9)**
- **Nomacopan inhibits different pathways to remdesivir and dexamethasone (SOC); potential to be additive**

Planned randomized clinical study design: Key considerations

- Randomize patients 2:1
- Patients on supplementary oxygen between 5-20 litres/minute
- Primary end point is time to normalisation of oxygen - easily measured using a pulse oximeter
- Nomacopan administered daily sub cutaneous for up to 14 days
- Key secondary end points to include need for intubation and assisted ventilation and survival
- Each individual study powered with circa 60 patients
- Nomacopan additive to current standard of care: dexamethasone and remdesivir where available

COVID-19 programs build on existing clinical experience in the use of nomacopan, including >35 cumulative patient-years of safety data with no reported drug related SAEs, and clinical responses across a range of inflammatory conditions in Phase 2 / Phase 3 development

Ongoing and planned COVID-19 pneumonia clinical programs



United Kingdom

- Observational biomarker study to identify COVID-19 patients suitable for nomacopan. Data collected on ~50 patients; sample analysis expected Q4 2020
- Ongoing longitudinal study: samples from patients with worsening disease
- Selected by AGILE platform

United States

- Initial proof of principle treatment in patients with COVID-19 pneumonia via expanded access programs
- Proposed multi-center investigator-led randomized study in regulatory submission

Brazil

- Recruitment completed into initial proof of principle treatment in patients
- Potential progression to randomized controlled study if review by Data and Safety Monitoring Board (DSMB) is successful

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