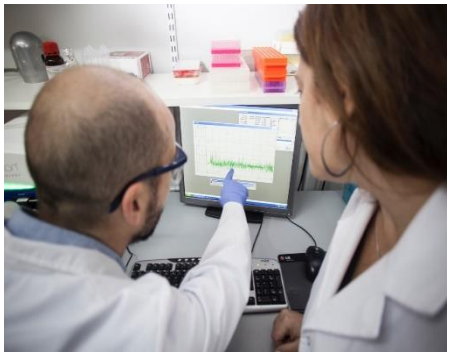
Fernando Goldbaum
August 11 2021

RBD-specific Polyclonal F(ab´)$_2$ fragments of equine antibodies improve survival in severe patients hospitalized with COVID-19

The Company

- R&D Biotech private company, founded in 2009 in Buenos Aires, Argentina
- Insud pharma is the main shareholder of the company
- It develops vaccines and products for human health.
- Inmunova's main technology:
  - IMC®: stands for Immuno Multi Carrier, a proprietary recombinant platform for vaccine delivery
  - Development of immunogens and therapeutic hyperimmune sera



Hemolytic Uremic Syndrome: a severe Orphan Disease

- **Hemolytic uremic syndrome (HUS)** occurs after an infection of the digestive tract by Shiga toxin *Escherichia coli (**STEC**)* bacterium, which might be found in **meat, dairy products, vegetables and juices**.

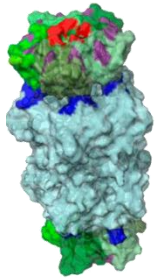
- **HUS** affects predominantly **children** and is a life-threatening disease characterized by acute renal failure (uraemia), haemolytic anaemia, and a low platelet count (thrombocytopenia)

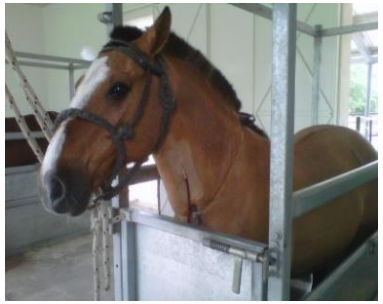
- It is a medical emergency with **5% mortality rate** and most common cause of sudden short-term-acute-kidney failure in children.

- **No current treatment exist for prevention or treatment of this disease**. Only supportive measures

INM-004 An innovative product to prevent the onset of HUS

IMC®- Stx Chimeras





- **Product:** Anti-Shiga toxin - by using a novel proprietary immunogen, we have generated equine immunoglobulin fragments that neutralize 8 variants of Shiga toxins.
- **Phase 1 clinical trial** succesfully finished during 2018
- **Phase 2/3 clinical trial** launched during 2019

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Orphan Drug status

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 April 2018 **CONFIDENTIAL**
EMA/COMP/39437/2018
EMA/OD/248/17
Committee for Orphan Medicinal Products

Opinion of the Committee for Orphan Medicinal Products on orphan medicinal product designation

Medicinal product

Active ingredient: Equine immunoglobulin F(ab')$_2$ fragments targeting Shiga toxin

Sponsor

Name or corporate name of sponsor: Chemo Research S.L.

Permanent address of sponsor: c/ Manuel Pombo Angulo, 28
3rd floor
28050 Madrid
Spain

Indication

Orphan indication: Prevention of haemolytic uraemic syndrome

Basis for opinion

Pursuant to Article 5 of Regulation (EC) No 141/2000 of 16 December 1999, Chemo Research S.L. submitted to the European Medicines Agency on 04 December 2017 an application for orphan medicinal product designation for the above-mentioned medicinal product.

The procedure started on 22 January 2018.

Written explanations were provided by the sponsor on 3 April 2018.

Oral explanations were given by the sponsor on 18 April 2018.

Opinion

1. The COMP, having considered the application in accordance with Article 5 of Regulation (EC) No 141/2000 of 16 December 1999, is of the opinion that:

- the medicinal product satisfies the criteria for designation as laid out in the first paragraph of Article 3(1)(a), Regulation (EC) No 141/2000 of 16 December 1999; and

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 Facsimile +44 (0)20 3660 5555
E-mail info@ema.europa.eu Website www.ema.europa.eu

FDA U.S. FOOD & DRUG ADMINISTRATION

Office of Orphan Products Development
Food and Drug Administration
WO32- 5295
10903 New Hampshire Avenue
Silver Spring, MD 20993

AUG 1 9 2019

Exeltis USA, Inc.
180 Park Avenue, Suite 101
Florham Park, NJ 07932

Attention: Sandy S. Suh, PharmD
Head of Regulatory Affairs (R&D)
ssuh@exeltis.com

Re: Designation request #DRU-2018-6444
Amendment Date: June 12, 2019
Amendment Received: June 13, 2019

Dear Dr. Suh:

This letter responds to your amended request submitted on behalf of Inmunova S.A. for orphan-drug designation of neutralizing equine anti-Stx hyperimmune immunoglobulin F(ab')2 fragment for "treatment of Shiga-toxin producing bacterial infection as it relates to the prevention of hemolytic uremic syndrome."

Pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb), your orphan-drug designation request of neutralizing equine anti-Stx hyperimmune immunoglobulin F(ab')2 fragment is granted for *treatment of Shiga-toxin producing bacterial infection as it relates to the prevention of hemolytic uremic syndrome*. Please be advised that it is the active moiety or principal molecular structural features of the drug[1] and not the formulation of the drug that is designated.

FDA U.S. FOOD & DRUG ADMINISTRATION

Food and Drug Administration
10903 New Hampshire Avenue
WO32- 5295
Silver Spring, MD 20993

Exeltis USA, Inc.
180 Park Ave, Suite 101
Florham Park, NJ 07932

Attention: Sandy S. Suh, Pharm.D.
Head of Regulatory Affairs (R&D)
ssuh@exeltis.com

Re: Designation request # RPD-2019-261
Dated: November 26, 2019
Received: December 2, 2019

Dear Dr. Suh:

This letter responds to your request on behalf of Inmunova S.A. for rare pediatric disease designation of equine immunoglobulin F(ab')2 fragments targeting Shiga toxin (NEAST) for "treatment of Shiga-toxin producing bacteria as it relates to the prevention of hemolytic uremic syndrome (HUS)."

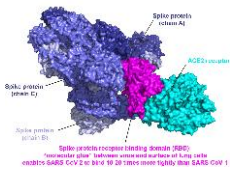
We hereby grant your request and designate NEAST for *prevention of hemolytic uremic syndrome (HUS) due to Shiga-toxin producing bacteria* as a drug for a "rare pediatric disease," as defined in section 529(a)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 360ff(a)(3)).

Based on information you provided and additional information garnered from the literature, there is sufficient information to demonstrate that acute renal failure, severe anemia, neurologic sequelae, and chronic renal disease are serious or life-threatening manifestations of HUS due to Shiga-toxin producing bacteria that primarily affect children. Therefore, your product is eligible for rare pediatric disease designation for prevention of HUS due to Shiga-toxin producing bacteria.

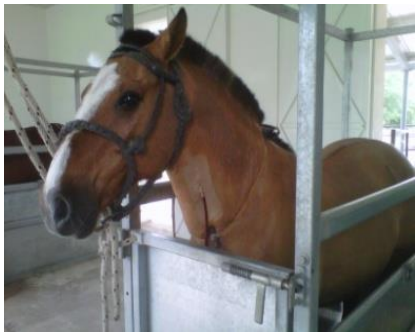
The statute requires that FDA, in responding to rare pediatric disease designation requests, decide whether the associated marketing application for the drug will be a "rare pediatric disease product application." Section 529(d)(3) of the FD&C Act (21 U.S.C. 360ff(d)(3)). At this time, we cannot designate any associated marketing application for the drug as a "rare pediatric disease product application," as defined in section 529(a)(4) of the FD&C Act (21 U.S.C. 360ff(a)(4)), because we cannot assess whether it will qualify as such until the time of approval or licensure. We can only conditionally designate the marketing

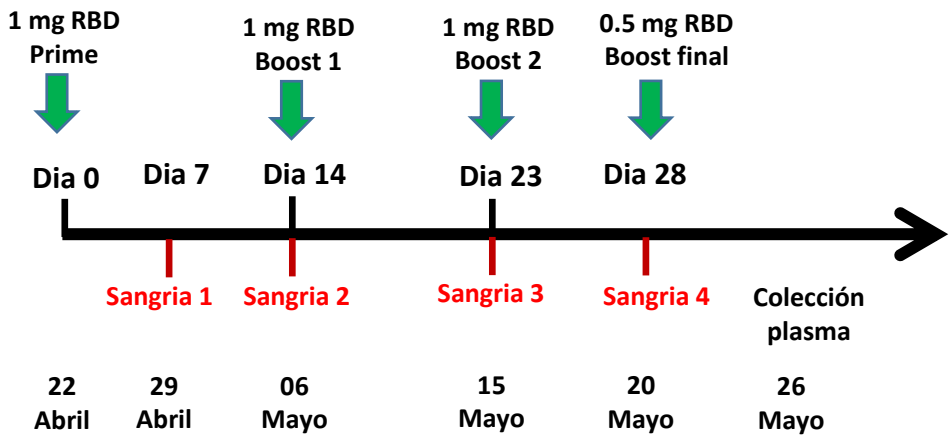
- April 2018 EMA grants ODD
- August 2019 FDA grants ODD
- February 2020 FDA grants Rare Pediatrics Disease designation.

Anti SARS-CoV-2 hyperimmune sera: a product based on previous developments



RBD





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bioL mAbxience From lab to life

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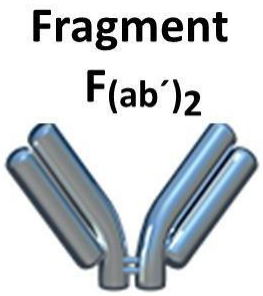
CoviFab® In vitro activity

- Neutralizing capacity of INM005 greater than 1/20,000 *in vitro*
- Absence of Fc fragment could prevent ADE and exacerbated inflammatory reactions



- Excellent safety profile: use in early stages of the disease
- Manufacturing process can be scaled up

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Phase II/

INM005 Arm 4 mg

n= 6

Placebo Arm

n= 6

EClinicalMedicine

Published by THE LANCET

RBD-specific polyclonal F(ab´)2 fragments of equine antibodies in patients with moderate to severe COVID-19 disease: a randomized, multicentre, double-blind, placebo-controlled, adaptive phase 2/3 clinical trial

Gustavo Lopardo, M.D.[1,2], Waldo H. Belloso, M.D.[3], Esteban Nannini, M.D.[4,5], Mariana Colonna, Bioch.[6], Santiago Sanguineti, PhD.[6], Vanesa Zylberman, PhD.[5,6], Luciana Muñoz, Bioch.[6], Martín Dobarro, M.D.[7], Gabriel Lebersztein, M.D.[7], Javier Farina, M.D.[8], Gabriela Vidiella, M.D.[9], Anselmo Bertetti, M.D.[10], Favio Crudo, M.D.[11,12], Maria Fernanda Alzogaray, M.D.[13], Laura Barcelona, M.D.[1], Ricardo Teijeiro, M.D.[14], Sandra Lambert, M.D.[15], Darío Scublinsky, M.D.[16], Marisa Iacono, M.D.[17], Vanina Stanek, M.D.[3], Rubén Solari, M.D.[18], Pablo Cruz, M.D.[19], Marcelo Martín Casas, M.D.[20], Lorena Abusamra, M.D.[21], Héctor Lucas Luciardi, M.D.[22], Alberto Cremona, M.D.[23], Diego Caruso, M.D.[24], Bernardo de Miguel, PhD.[25], Santiago Perez Lloret, PhD.[5,26,27], Susana Millán, M.D.[25], Yael Kilstein, M.D.[28], Ana Pereiro, M.D.[29], Omar Sued, M.D.[30], Pedro Cahn, M.D.[30], Linus Spatz, Lic.[6], Fernando Goldbaum, PhD.[5,6,31,32], on behalf of INM005 Study Group†.

Final analysis

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Albeit not having reached the primary endpoint, we found clinical improvement of hospitalized patients with SARS-CoV-2 pneumonia, particularly those with severe disease.

Outcomes	INM005 (N=118)	Placebo (N=123)	Risk difference or Hazard Ratio (95% CI)	p-value
Primary outcome				
Improvement in at least two categories in WHO ordinal clinical scale at day 28 or discharge	106 (89·8%)	104 (84·5%)	Risk difference, 5·28% (-3·95 to 14·50)	0·15
Secondary outcomes				
Time to achieve improvement in at least two categories on the ordinal clinical scale (days)	14·2 ± 7	16·3 ± 0·7	1·31 (1·00 to 1·74)	0·05
Improvement in at least two categories in WHO ordinal clinical scale at day 28* (%)	87·3 ± 3·1	79·7 ± 3·6	··	0·08
Improvement in at least two categories in WHO ordinal clinical scale or discharge at day 7* (%)	64·1 ± 4·4	58·3 ± 4·5	··	0·26
Improvement in at least two categories in WHO ordinal clinical scale or discharge at day 14 *(%)	87·3 ± 3·1	79·7 ± 3·6	··	0·05
Time until discharge (days)	8·7 ± 0·6	10·2 ± 0·7	1·26 (0·96 to 1·66)	0·09
Improvement in the ordinal scale for clinical status scale (AUC)**	60·5 ± 41·7	73·7 ± 49·4	-13·14 (-1·56 to -24·72)	0·02
Mean category at day 7***	3·1 ± 1·7	2·7 ± 1·7	0·63 (0·36 to 1·13)	0·19
Mean category at day 14***	2·4 ± 2·2	1·7 ± 1·8	0·52 (0·29 to 0·96)	0·03
Mean category at day 21***	2·1 ± 2·3	1·5 ± 1·9	0·54 (0·30 to 0·99)	0·05
Mean category at day 28***	1·9 ± 2·5	1·4 ± 2·1	0·80 (0·44 to 1·46)	0·99
Time until discharge from ICU (days)	24·7 ± 0·8	23·6 ± 0·8	0·67 (0·35 to 1·28)	0·22
Patients requiring ICU admission at day 28* (%)	12·7 ± 3·1	17·8 ± 3·5	··	0·11
Patients requiring invasive mechanical ventilation at day 28* (%)	9·3 ± 2·6	13·9 ± 2·9	··	0·20
Overall mortality* (%)	6·9 ± 2·3	11·4 ± 2·9	··	0·19
Risk to disease progression***	17 (14·4%)	29 (23·5%)	0·54 (0·28 to 1·05)	0·07

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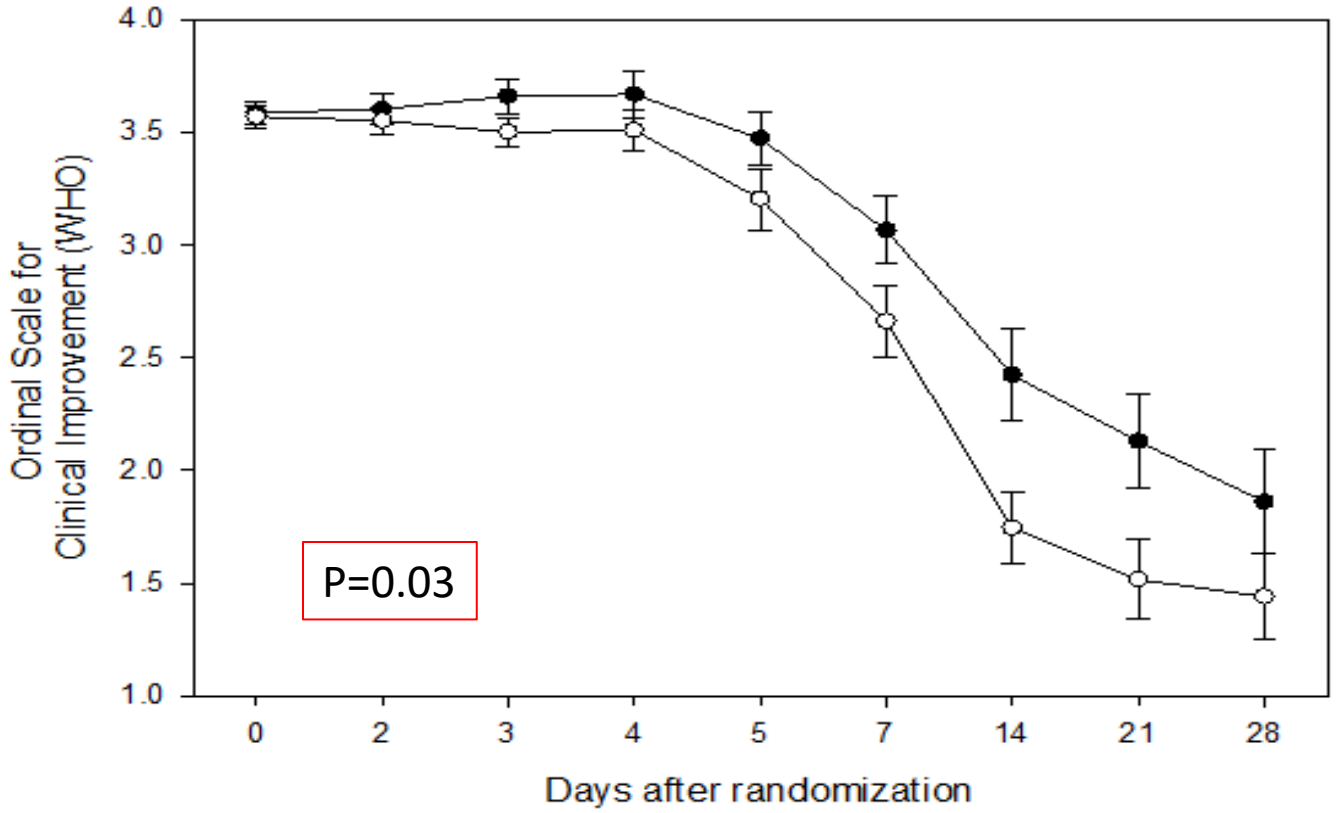
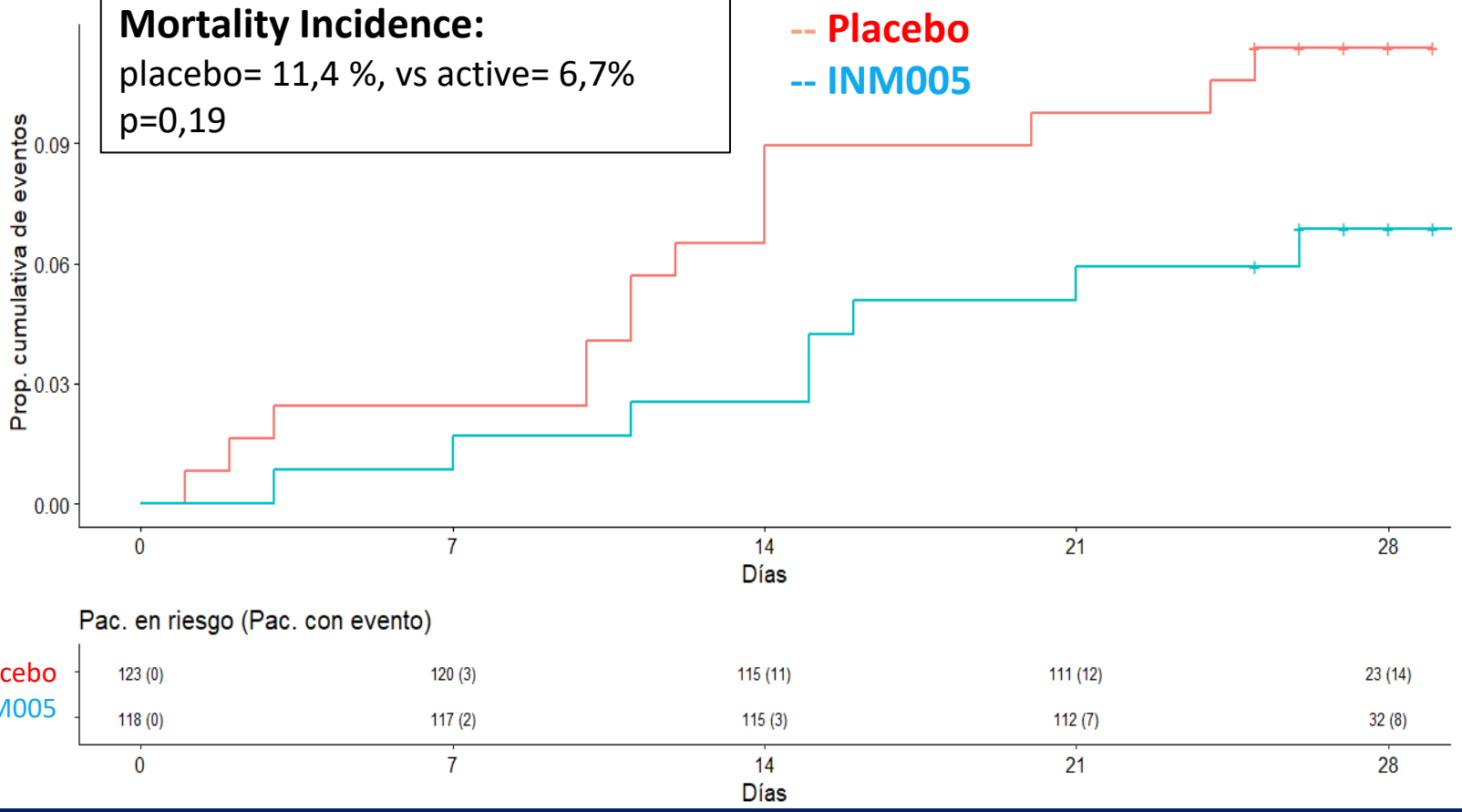
Patient trends on the WHO scale



- The area under the curve of the WHO scale values was significantly lower in the INM005 group than in the placebo
- The average of the WHO scale shows on day 7 an improvement in patients who received INM005, the difference increases to 14 and 21 days (odds ratio [95% CI]: 0·63 [0·36-1·13], 0·53 [0·29-0·96], and 0·54 [0·29-0·99], respectively).

Mortality

Mortality Incidence:
placebo= 11,4 %, vs active= 6,7%
p=0,19



- No significative difference in mortality incidence
- Mortality decreases a 39% in the active arm compared with placebo

Conclusions

- Findings in the study population treated with INM005
  - No statistically significant difference in the improvement of 2 points or discharge at day 28 (primary endpoint)
  - Statistically Significant clinical improvement throughout the 28-day period of the clinical trial.
  - Statistically Significant improvement of 2 points in the WHO scale at days 14 and 21.
  - Statistically significant difference in time to achieve improvement in at least 2 points in the WHO scale or discharge (16 vs 14 days)
  - A Statistically Significant decrease in the number of events associated to the progression of COVID-19 in 33% of the patients.
  - **A decrease of 39% in the mortality rate**
  - **A decrease of 33% in the number of ICU admissions.**
  - **A decrease of 36% in the requirement of MV.**

- Adequate safety profile, according to the products $F(ab')_2$

In November 2020 we were at a difficult crossroads

A single RCT showing clear trends

What to do?

A new RCT???

The RCT testing cocktail of mAbs in severe patients using the Recovery platform began on September 2020 and finished on June 2021

In the case of Inmunova we could get probably a nice paper but little practical application

Ask for EUA and increase data on safety and efficacy of our immunotherapy in “real life”

Excelent safety profile, choice to benefit thousands of patients, observational studies

ANMAT granted the EUA of CoviFab® to treat hospitalized COVID-19 severe patients on December 2020

- **Drug traceability**
- **Informed consent**
- **Approval for 1 year**

Plan for monitoring efficacy and safety of CoviFab® in a web-based platform

- List of patients and adverse events
- Efficacy assessment at day 21 post treatment
- Time to event: hospital stay, disease progression, and hospital discharge
- Proportion of patients requiring ICU, MV and deaths
- Data about clinical improvement

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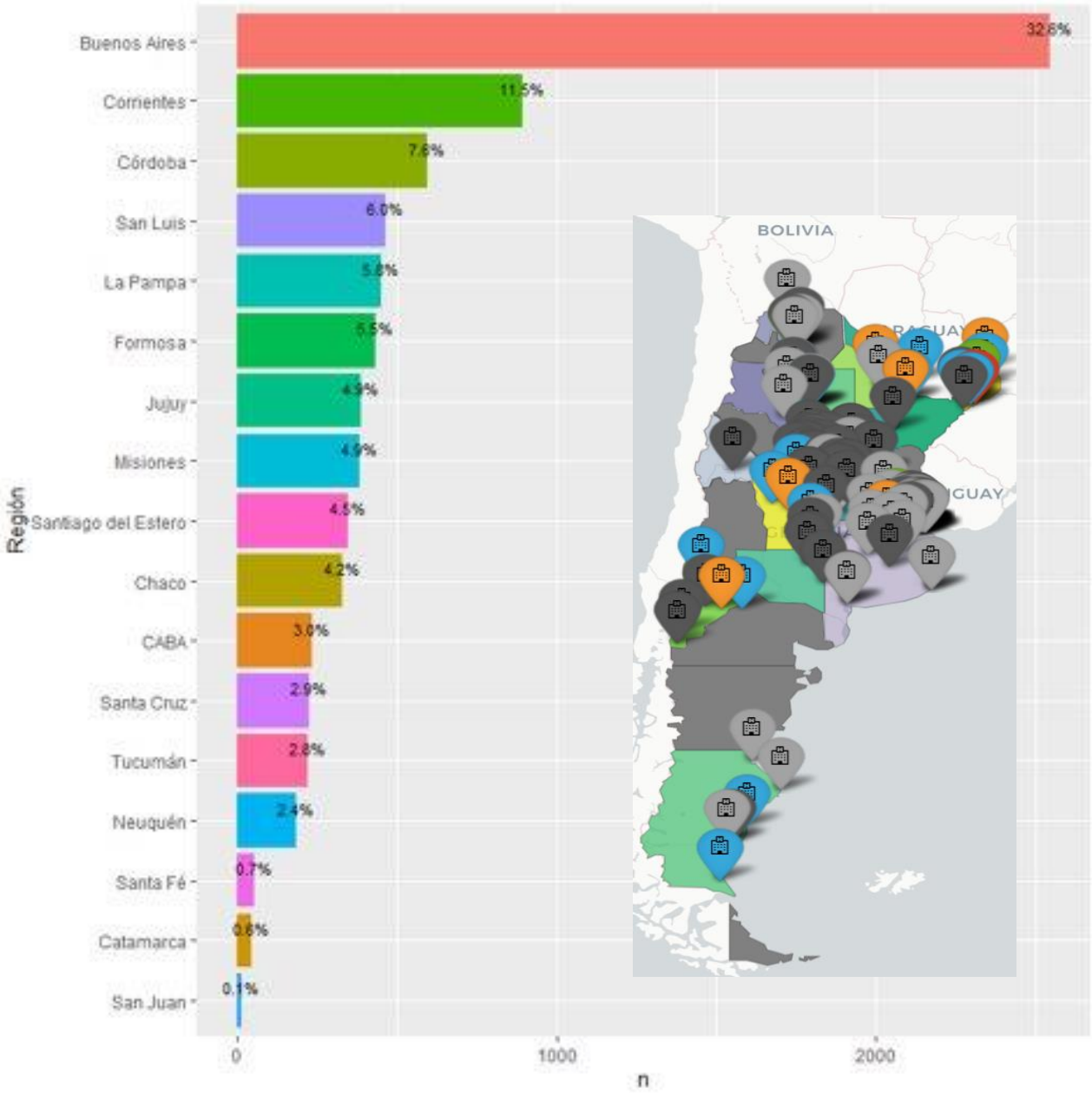
Patients treated with CoviFab® February to August 10 2021

- 17 states

- 221 health institutions

- 8,501 patients registered

- According to projections most than 20,000 treated patients



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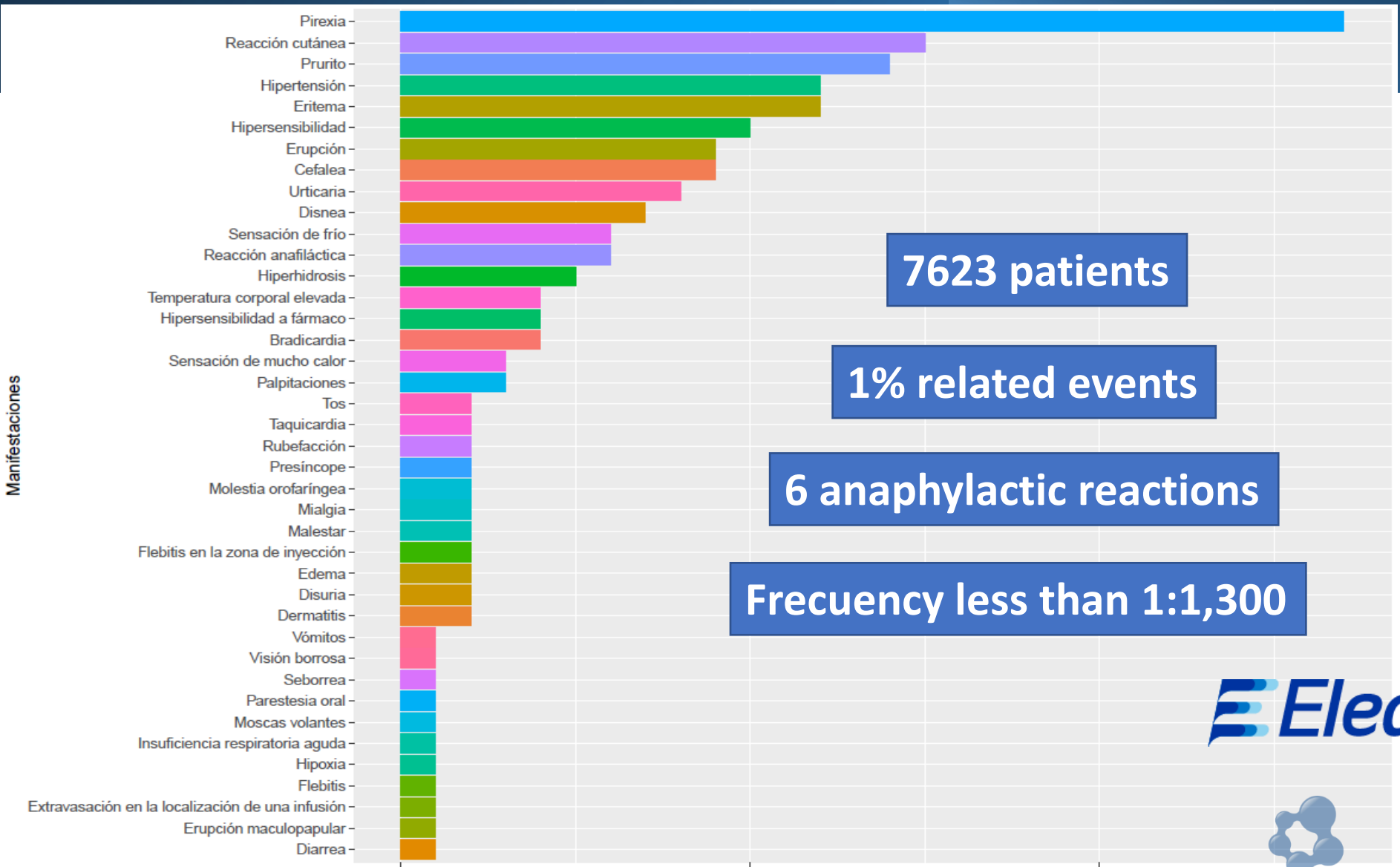
CoviFab® shows an excelent safety profile
Related events



7623 patients

1% related events

6 anaphylactic reactions

Frecuency less than 1:1,300

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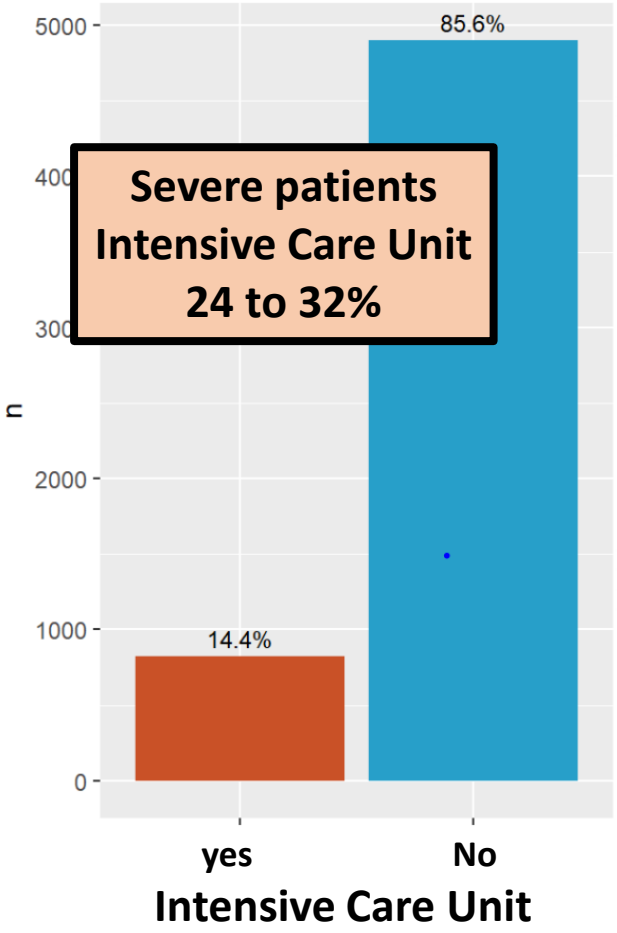
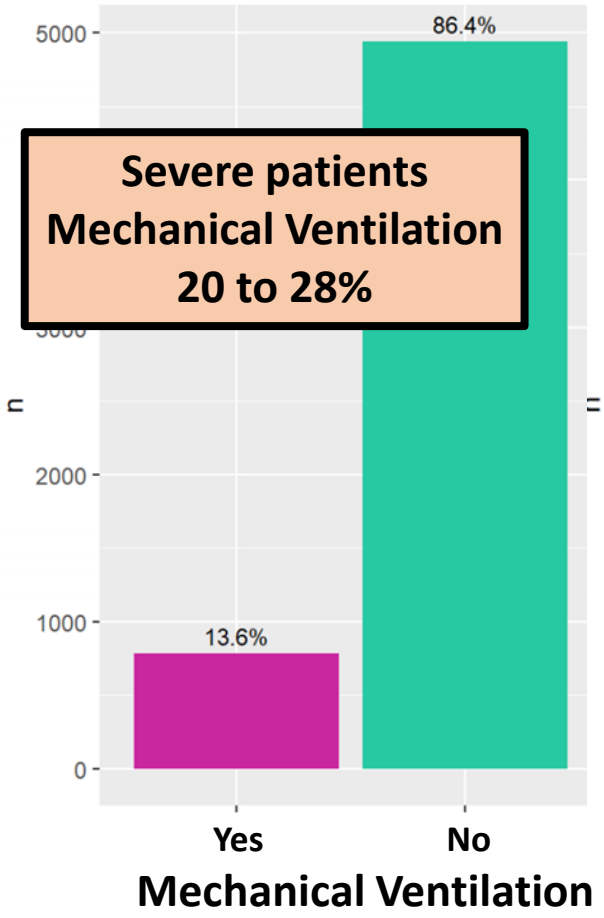
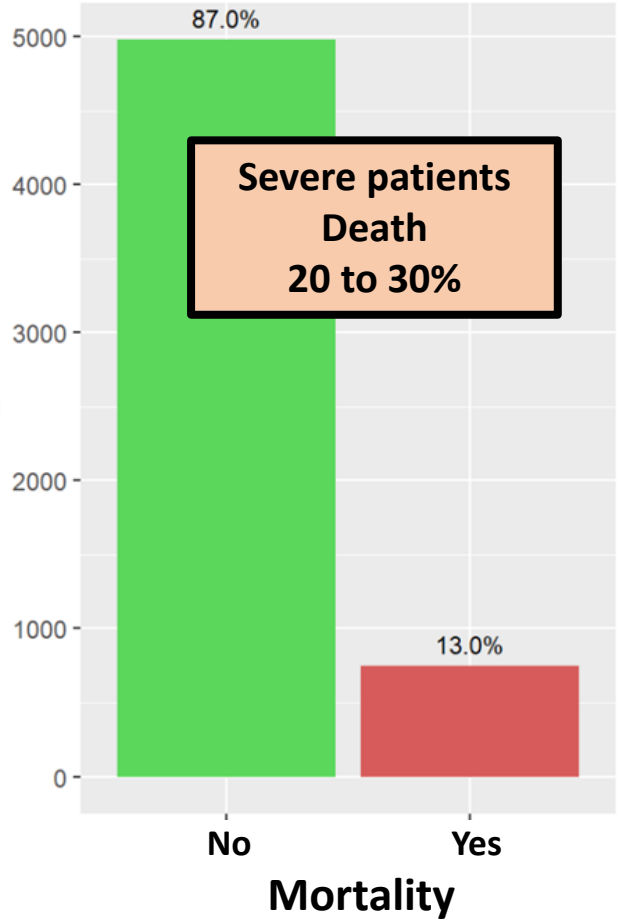
21-day cohort with closed data
5.722 patients, 86% Severe



Severe patients
Intensive Care Unit
24 to 32%



Severe patients
Mechanical Ventilation
20 to 28%



Severe patients
Death
20 to 30%

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Efectiveness and Safety of CoviFab® after ANMAT´s EUA

Retrospective Cohort Study

- Htal. Campaña Corrientes
- 400 severe patients treated with CoviFab® vs 400 historic controls

  Feb-April 2021 Dec 2020- Jan 2021
- Primary Endpoint: Mortality
- Secondary Endpoints: ICU %, MV %
- Results: next days

HOSPITAL ITALIANO
de Buenos Aires
Departamento de Investigación

Elea

INMUNOVA

nature medicine

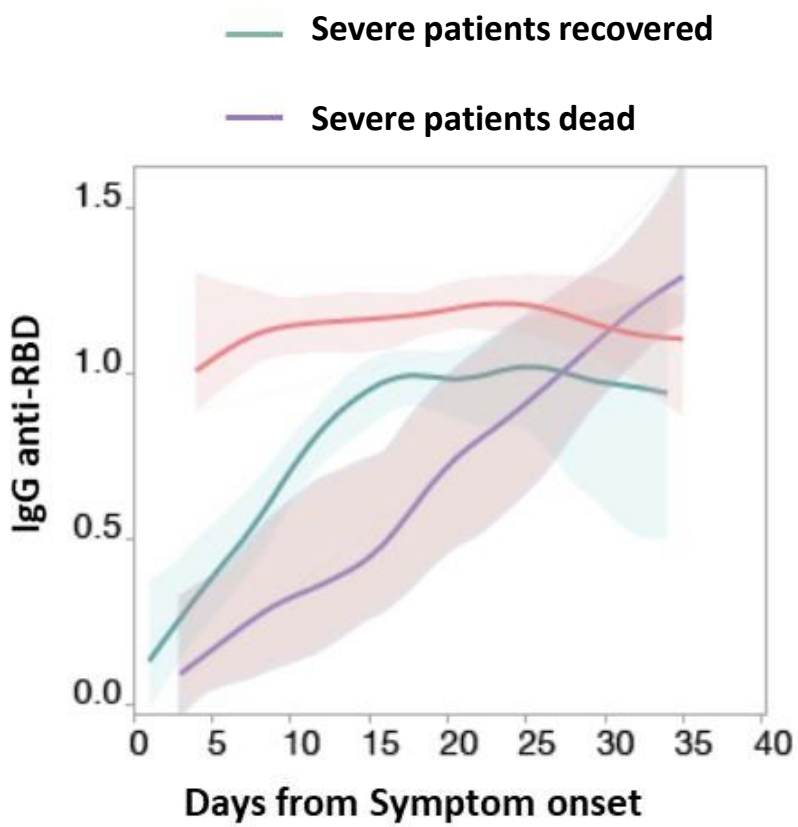
ARTICLES

https://doi.org/10.1038/s41591-021-01355-0

Check for updates

Delayed production of neutralizing antibodies correlates with fatal COVID-19

La aparición tardía de Acs neutralizantes correlaciona con la falta de clearence viral en pacientes fallecidos (*Lucas et al., Yale School of Medicine,* https://doi.org/10.1101/2020.12.18.20248331)



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Seronegative severe patients would most benefit from passive immunotherapies

Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial

Running title: REGEN-COV for COVID-19

RECOVERY Collaborative Group*

EClinicalMedicine 34 (2021) 100843

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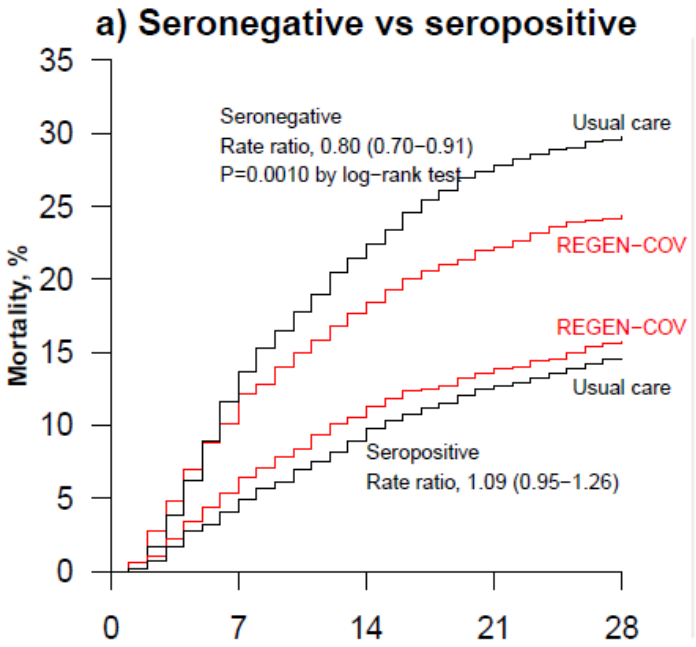
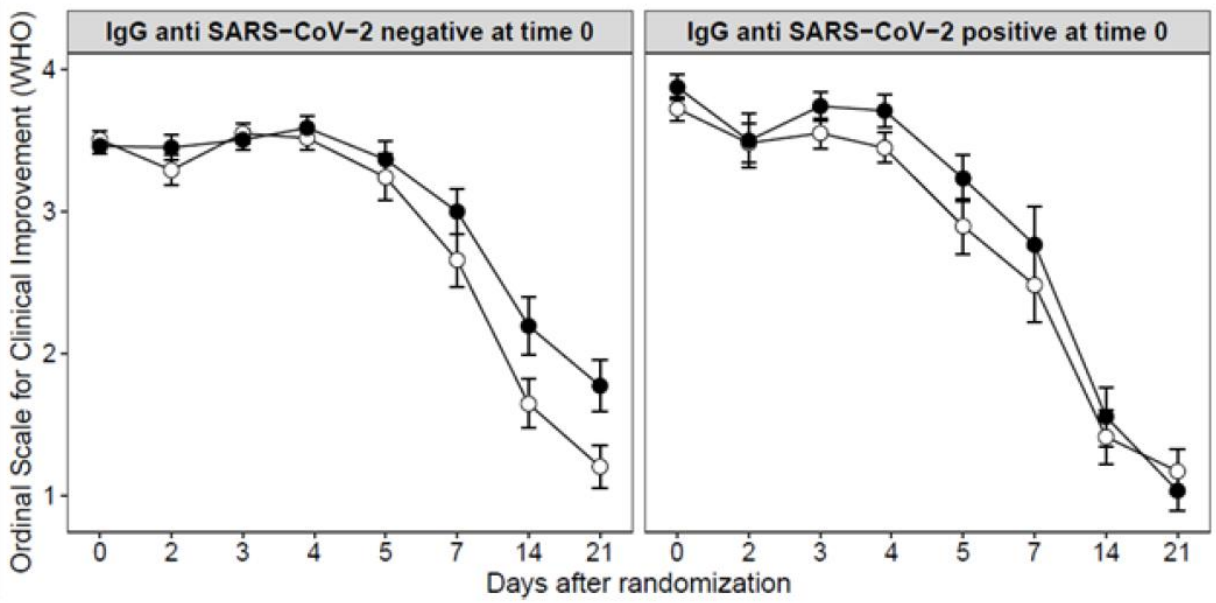
journal homepage: https://www.journals.elsevier.com/eclinicalmedicine

Research Paper

RBD-specific polyclonal F(ab')$_2$ fragments of equine antibodies in patients with moderate to severe COVID-19 disease: A randomized, multicenter, double-blind, placebo-controlled, adaptive phase 2/3 clinical trial





General Conclusions

- Real world data exhibit a trend very similar or better to that observed in the clinical trial, with the number of patients being treated now is 70 times higher.
- In the nex days we will be confirming this trend with a retrospective cohort study.
- CoviFab® *in vitro* neutralizes variant P.1 (Manaus) and variant B.1.1.7 (UK) with a similar capacity to the pandemic variant.
- CoviFab® is a safe product that meets the challenges of the current pandemic situation.

ANMAT decision to grant EUA for CoviFab® was right

Elea

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Thanks!

Questions?

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