Project No. 101045956

Biomarker and AI-supported FX06 therapy to prevent progression from mild and moderate to severe stages of COVID-19

Deliverable D1.8 – Report on collaborations and impact assessment

WP1 – Project management and collaboration with other initiatives

Lead Participant	GUF
Contributors	GUF
Delivery date	31/01/2022
Dissemination level	Public
Type	Report

Version 01

Funded by the European Union

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Revision history

Date	Authors	Revision
18.01.2022	Regina Minazhetdinova (GUF)	Draft version
24.01.2022	Benjamin Ginski (GUF)	Revision 1
25.01.2022	Andreia Cruz (accelCH)	Revision 2
31.01.2022	Benjamin Ginski (GUF)	Final version

Abstract

About 14% of COVID-19 patients with mild or moderate disease develop severe symptoms and are eventually admitted to the intensive care unit. The main goal of the COVend project is to reduce the number of COVID-19 patients in hospitals and thereby reduce the burden on patients and their families, hospital staff, and the healthcare sector. The specific objectives are, first, to enrich the current portfolio of SARS-CoV-2/COVID-19 prophylactics and therapeutics by clinically testing FX06 as a promising drug candidate. Second, to provide effective therapy against SARS-CoV-2 by using innovative immune biomarker profiling, endothelial cell assessment methods, and artificial intelligence driven models for decision support for clinical treatment of COVID-19 disease. This is expected to prevent a progression to severe disease and subsequent hospitalization.

Endothelial cells are the main regulators of vascular homeostasis (dynamic equilibrium), as they interact with both circulating cells and cells present in the vessel wall. When endothelial function deteriorates, vascular homeostasis is impaired, leading to increased permeability for blood and its components as well as inflammation of the endothelium. FX06 has shown to have a protective effect on the endothelium by reducing the inflammatory process. This way, the disease progress will be interrupted, resulting in faster recovery of the patients and less admissions to intensive care units.

Table of Contents

Partner short names

GUF	Johann Wolfgang Goethe Universität Frankfurt am Main
accelCH	accelopment Schweiz AG
F4	F4 Pharma GmbH

Abbreviations

D	Deliverable
DoA	Description of Action
EC	European Commission
EU	European Union
FAIR	Findable, Accessible, Interoperable, Reusable principles
HEU	Horizon Europe
ROS	Reactive oxygen species
T	Task
WP	Work Package

Executive Summary

The deliverable D1.8 is part of **Work Package (WP) 1 – Project management and collaboration with other initiatives** and shall report about the first activities with other research and innovation initiatives and all the established contacts. A brief outcome of the meeting with the European COVID-19 clinical trial network for therapeutics was considered.

During the grant agreement preparation phase, the European Commission (EC) has requested the addition of deliverable D1.6, due in month 3 of the project. This deliverable would be a "Report on virtual meeting with the other successful projects working on COVID-19 therapeutics funded under the Horizon Europe call "HORIZON-HLTH-2021-CORONA-01"". The instructions received at the time by the EC indicated that "… a preceding virtual meeting has to be set up by DG RTD and HaDEA to get to know other projects of the European COVID-19 clinical trial network". Despite of our efforts to contact the EC for more information, no virtual meeting has been scheduled so far. It can be assumed, that the EC can facilitate the network between the consortia of all the successful projects within this call, as it was expected. Nevertheless, all COVend partners intend to follow-up on other consortia and complementary initiatives in parallel, until new instructions are received by the EC. This deliverable identifies potential contacts and synergies that could be further developed in the future course of the project.

1 Introduction

Since the first cases in December of 2019, there have been over 260 million confirmed cases of COVID-19 worldwide, up to 11% of which become critically ill. Specifically, the endothelium is weakened by COVID-19 disease and requires an enormous amount of therapy to regenerate it. [2] According to the current knowledge however, there is no drug available at this time that has a positive effect on the regeneration of the endothelium and thus influences the progression of COVID-19 disease in such a way as to preventively reduce severe disease progression. COVend is a 3-year project that aims to change that by testing the promising drug FX06 against COVID-19. However, COVend is not the only EU project actively involved in the fight against the pandemic. Other successful projects were approved under the same call topic, as described in more detail below. To increase the outreach of the project results, it is essential to follow-up on other initiatives and explore synergies with relevant consortia.

1.1 Purpose and scope of the deliverable & Outcomes

The aim of deliverable D1.8: "Report on collaborations and impact assessment", is to **describe the activities with other research and innovation initiatives and established contacts, as well as an impact assessment of these. Since the project is still in an initial stage, updates on this topic will be considered in the reporting periods and in the further course of the project. In the course of the project, the coordinator will contact the European COVID-19 clinical trial network for therapeutics (covid19trials.eu) to identify opportunities for collaboration.** The present deliverable explores the potential collaborations between the different funded projects, especially to:

- Exchange experience and knowledge (e.g. latest therapeutic approaches and insights into COVID-19 research);
- Establish possible cooperation strategies leading to a more effective bundling of the workload (less resources needed) and higher quality research results (greater expertise from different project partners);

In the Description of Action (DoA), these objectives are considered in both Work Package 1 and 8 (WP1, WP8).

1.2 Open Science strategy

The Horizon Europe projects are meant to "open up science". The research outputs must be shared openly, re-used and stimulate new transdisciplinary/trans-sectoral collaborations.[1]" Thus, the COVend consortium is committed to open access publishing, following the guidelines outlined by the European Commission and the available guidelines for open access in COVID-19 projects. The COVend consortium aims to maximise the impact of its project results by sharing its research results as widely and as openly as possible, as soon as possible. The practices will include:

- Open methodology, to make our research comprehensible and reproducible for external researchers;
- Producing open-source AI-tools, for possible modification and redistribution via the GitHub platform;

[1] European Commission, Directorate-General for Research and Innovation, A new horizon for Europe : impact assessment of the 9th EU framework programme for research and innovation, Publications Office, 2018, https://data.europa.eu/doi/10.2777/978720

[2] European Heart Journal (2020) 41, 3038–3044 doi:10.1093/eurheartj/ehaa623

- Participating in the EU Open Research Data scheme adhering to EC's rules. It will especially be taking care to apply the Findable, Accessible, Interoperable, Reusable (FAIR) principles to the data collected within the project;
- Open access and review guaranteeing free access to all peer-reviewed publications and sharing them on our website;
- Open educational resources, encompassing training materials developed as part of the clinical trial.

COVend will follow the EU's open science policy to ensure that our scientific process and practices focus on spreading knowledge to a broad range of interested audience.

In this sense, the COVend consortium will, to the best of its knowledge and belief, take the possible steps to make the research results available to the EU and thereby increase the interest of other initiatives and consortia in our project.

The EC supports various initiatives for data sharing and analysis in an effort to accelerate coronavirus research, such as the European COVID-19 Data Platform. The COVend partners will consider these as well and will also take into account the recommendations from the Research Data Alliance COVID-19 Recommendations and Guidelines for Data Sharing when possible.

2 Meeting with European COVID-19 clinical trial network

According to deliverable D1.6 "Report on virtual meeting with the other successful projects working on COVID-19 therapeutics funded under the Horizon Europe call", "HORIZON-HLTH-2021-CORONA-01", a preceding virtual meeting has to be set up by DG RTD and HaDEA to get to know other projects of the European COVID-19 clinical trial network.

However, a virtual meeting was not set up yet and therefore no exchange between other project partners could be initiated. For this reason, the COVend team alternatively plans to reach out to these project partners aside from a planned virtual meeting.

3 Relevant Projects - Identification

The COVend partners have a large interest to exchange information and develop a close cooperation with other COVID-19 funded projects. In this regard, a search resulted in five projects which could be found to have potential for a collaboration:

- ECRAID-PRIME;
- ExeVir- XVR011;
- HIPRA Scientific – RDBCOV;
- Fabentech - EPIC-CROWN-2;
- MetrioPharm AG – iMPact.

These projects were funded in the same call topic as COVend: "HORIZON-HLTH-2021-CORONA-01-01, Vaccines & therapeutic clinical trials to boost COVID-19 prevention and treatment". The common goal

for all five projects is the development of promising therapeutic or prophylactic candidates against SARS-CoV-2/COVID-19, aiming at treating mild to moderate illness. An overview of these projects is presented in Figure 1.

Acronym	Title	Lead partner	Partners
VACCINES & THERAPEUTIC CLINICAL TRIALS TO BOOST COVID-19 PREVENTION AND TREATMENT – EU funding: € 57 million			
ECRAID-PRIME	European Clinical Research Alliance on Infectious Diseases - PRIMary care adaptive platform trial for pandemics and Epidemics	Universitair Medisch Centrum Utrecht (NL)	4 partners: BE, FR, NL, UK
XVR011 Phase 2	ExeVir's XVR011, a best in class nanobody-based biology that broadly neutralizes SARS-COV-1 and SARS-COV-2	ExeVir Bio (BE)	5 partners: BE, DE, FR, IE
RBDCOV	RBD Dimer recombinant protein vaccine against SARSCoV2	HIPRA Scientific (ES)	13 partners: BE, DE, ES, IT, TR, UK
EPIC-CROWN-2	Equine Polyclonal antibodies Immunotherapy against COVID-19/SARS-CoV2-VOC	Fabentech (FR)	5 partners: DE, EL, ES, FR
iMPact	Novel, orally available immune modulator MP1032 with anti-SARS-CoV-2 and anti-cytokine activity	MetrioPharm AG (CH)	4 partners: AT, CH, DE, NL
COVend	Biomarker and AI-supported FX06 therapy to prevent progression from mild and moderate to severe stages of COVID-19	Johann Wolfgang Goethe Universitaet Frankfurt-am-Main (DE)	18 partners: AT, BE, CH, DE, ES, FI, FR, IE, IT, LT, NL, PT, RO, SI,

Figure 1 – Projects approved under the call topic HORIZON-HLTH-2021-CORONA-01-01

3.1 ECRAID-PRIME

3.1.1 Project Information

The European Clinical Research Alliance on Infectious Disease: PRIMary care adaptive platform trial for pandemics and Epidemics (ECRAID-PRIME) was first launched on 1 December 2021. The project aims to reduce the impact of infectious diseases on individual and population health. The primary aim of ECRAID-PRIME is clinical research supported by laboratory, epidemiological and statistical analyses, data management, biobanking, training and public engagement. It is the first European Adaptive Platform Trial on COVID-19 therapeutics in the primary care setting and has a long partnership with renowned universities from Belgium, France, UK, Germany, Spain, Italy, Hungary, and the Netherlands (see also figure 3 and 4 for more details). The project is led by the University Medical Centre Utrecht in The Netherlands. The focus is on early phase clinical trials for therapeutics and in the identification of therapeutics for Phase III trials. The platform will make use of response adaptive randomization to ensure that the safety and efficacy of treatments can be assessed in the timeliest manner. Further information on the ECRAID-PRIME project can be found on their website (https://www.ecraid.eu) (see also figure 2).

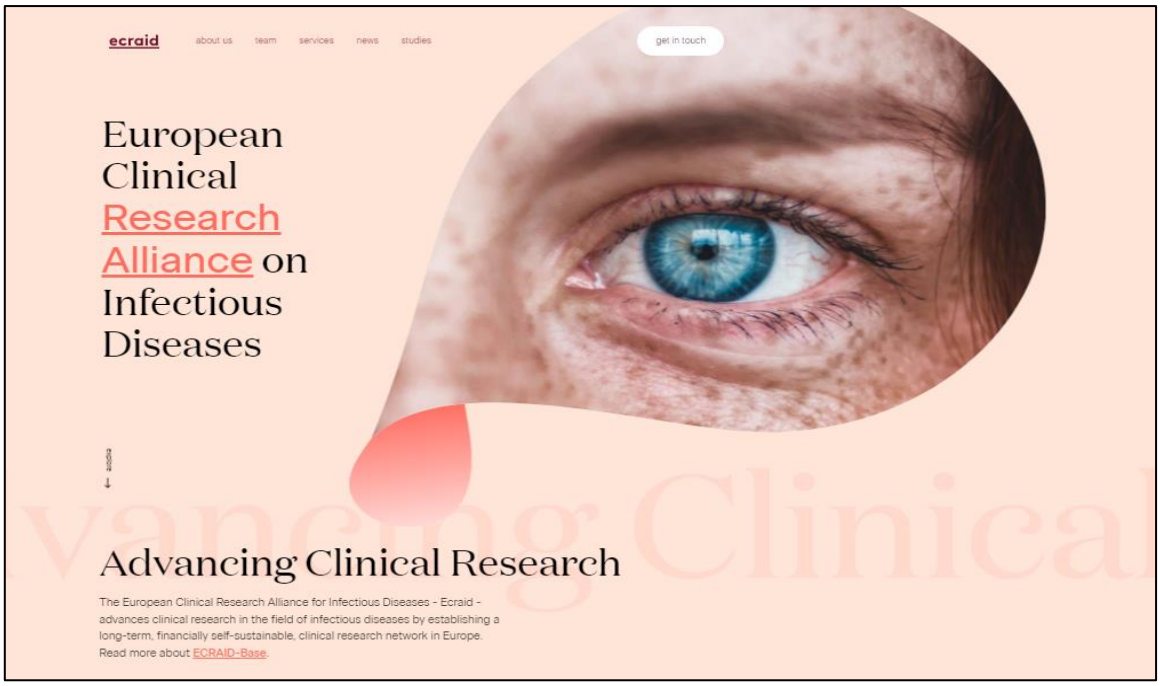

Figure 2 – Website ECRAID-PRIME (https://www.ecraid.eu/ecraid-prime).

3.1.2 Cooperation

ECRAID-Prime will select and evaluate novel approaches for community treatment of COVID-19. Since there are currently fewer opportunities for people to find treatments that speed up recovery and reduce the need for hospital admission in the first place, it can be assumed that COVend could become a valuable contributor to the research network. In this sense, an increase of the outreach of the COVend project would certainly be possible and ECRAID-PRIME would benefit from a competent research partner on their platform.

Figure 3 - Partner ECRAID-PRIME (part 1).

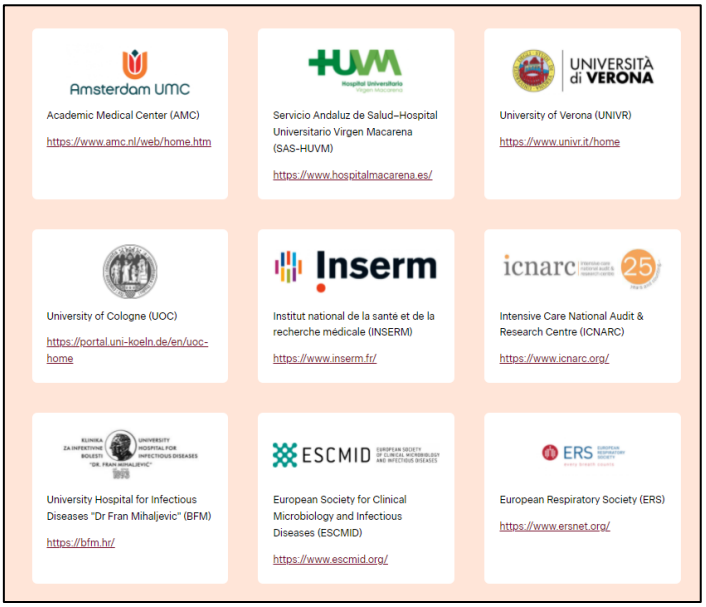

Figure 4 - Partner ECRAID-PRIME (part 2).

3.2 ExeVir - XVR011

3.2.1 Project Information

ExeVir is a Belgium clinical stage company which develops single-domain antibody-based therapies against COVID-19. The most promising candidate to neutralize SARS-CoV-2 is XVR011. XVR011 is currently in Phase 1b/2 clinical study EXEVIR0101. The study evaluates the safety and efficacy of the antibody in neutralizing the SARS-CoV-2 virus in hospitalized patients with mild to moderate COVID-19 symptoms. ExeVir collaborates with Prof. Xavier Saelens and Prof. Nico Callewaert from VIB-Ghent University to progress research on new antiviral VHH antibodies. ExeVir has partnerships collaborations in Belgium, Germany, France, and Ireland. Further information on the company and the project can be found on their website (https://exevir.com/) (see also figure 5-7).

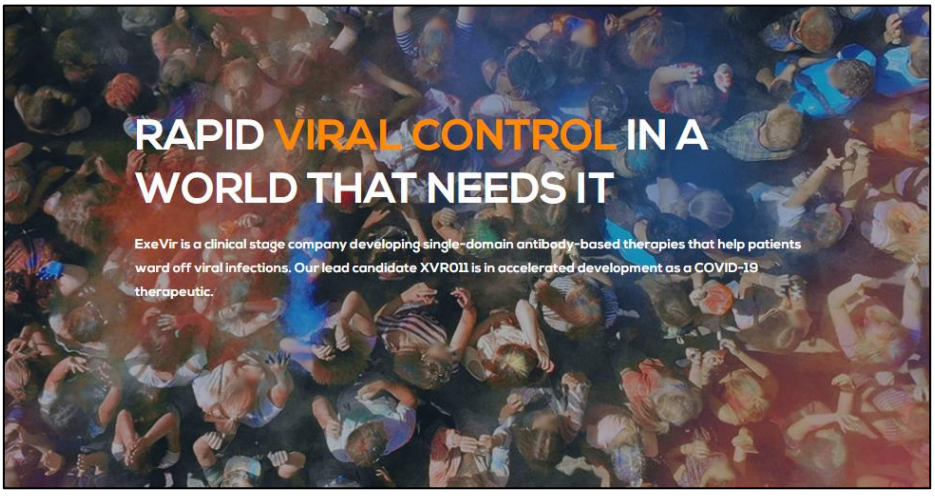

Figure 5 – Website ExeVir (https://exevir.com/).

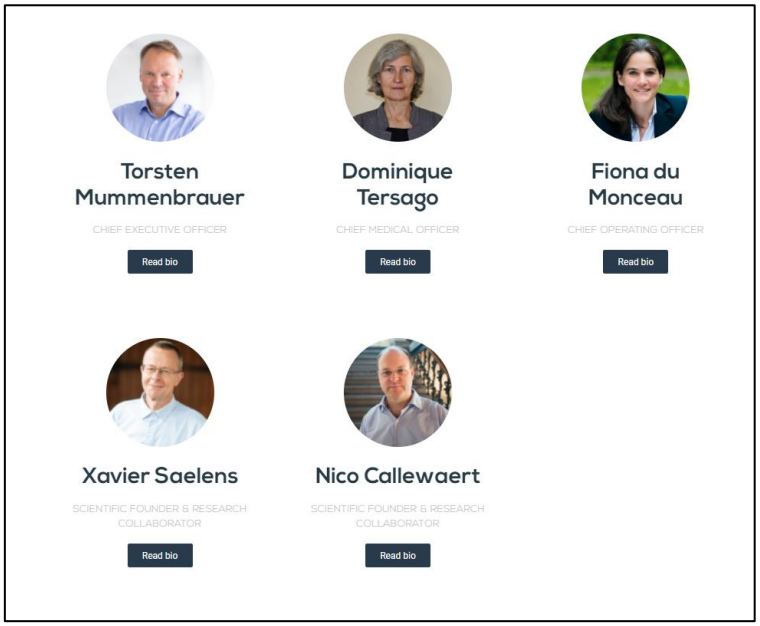

Figure 6 – Partner ExeVir (part 1).

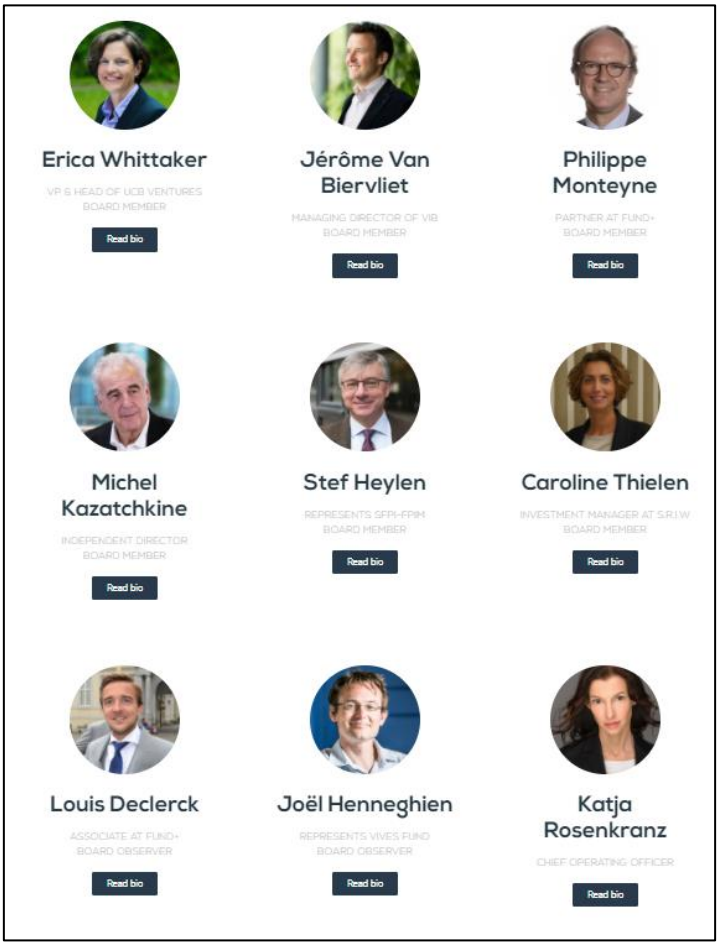

Figure 7 - Partner ExeVir (part 2).

3.2.2 Cooperation

In September 2021, ExeVir announced that the first patient has been treated in a Phase 1b/2 global clinical study of XVR011. EXEVIR0101 is a two-part study: phase 1 will inform and broaden the safety database for XVR011 as well as provide important antiviral and clinical activity data before the current study proceeds to phase 2, which will evaluate both efficacy and safety. While FX06 positively influences the healing process of the endothelium, XVR011 directly uses antibodies to neutralise the SARS-CoV-2 virus. Both drugs therefore target different therapies and it is conceivable that the drugs may be administered in combination in the future. XVR011 is directly interacting with the virus while FX06 is targeting the host response. Although the two drugs have very different targets they may act synergistically.

3.3 HIPRA Scientific – RBDCOV

3.3.1 Project Information

The Spanish company HIPRA Scientific leads the project "RBD Dimer recombinant protein vaccine against SARSCoV2" (RBDCOV). It is developing a vaccine based on a recombinant protein designed to induce a powerful neutralizing immune response to the Covid-19 virus which is capable of providing high levels of safety. The vaccination strategy of RBDCOV contemplates the different scenarios: primary vaccination, effectiveness against different variants of the virus and the revaccination dose, as it is not an Adenovirus vector vaccine. The project encompasses 13 partners from Belgium, Germany, Spain, Italy, Turkey, and UK. Further information on the HIPRA project can be found on their website (https://www.hipracovid19.com/en/ (see also figure 8).

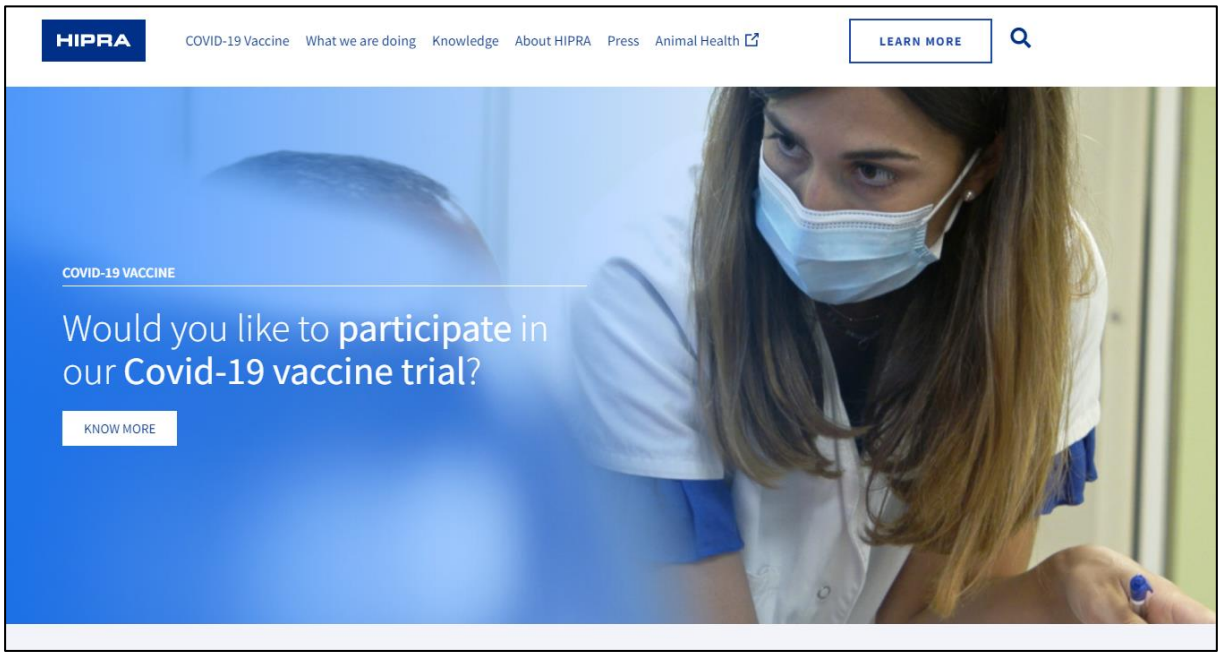

Figure 8 – Website HIPRA Scientific - RDBCOV (https://www.hipracovid19.com/en/).

3.3.2 Cooperation

While FX06 positively influences the healing process of the endothelium, RBDCOV provides a powerful immune response to neutralize the SARS-CoV-2 virus. Both drugs therefore target different therapies. For this reason, there is no direct interaction and a synergistic activity is not foreseen.

3.4 Fabentech - EPIC-CROWN-2

3.4.1 Project Information

The Equine Polyclonal antibodies Immunotherapy against COVID-19/SARS-CoV2-VOC (EPIC-CROWN-2) project is driven by the French company Fabentech as part of a consortium of five partners from Germany, Spain, Greece and France. The project aims to rapidly assess the clinical benefits of its polyclonal antibody treatment called FABENCOV against SARS-CoV-2. The treatment targets at-risk patients with moderate to severe symptoms of respiratory distress and has already shown promising preclinical efficacy against the main COVID-19 variants. The project is currently starting a multi-centre Phase II a/b study on 400 patients in four European countries. Additionally, *in vitro* and *in vivo* studies will further assess the neutralizing ability of FABENCOV (see figure 9-11).

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Fab'entech, Winner in an Ambitious European Programme, Has Been Awarded 9.2 Million Euros to Develop Its Treatment against Covid-19 and its Variants

December 13, 2021 12:16 PM Eastern Standard Time

LYON, France--(BUSINESS WIRE)--**The EPIC-CROWN-2 project, initiated by Fab'entech (Lyon-based biotech company), has received funding to the tune of 9.2 million euros from the European Commission. Thanks to this grant, awarded in the context of the first call for HERA projects (HERA is a new European authority dedicated to preparing and responding to health emergencies), Fab'entech will be able to accelerate the development of its clinical programme in order to provide, as rapidly as possible, its treatment against SARS-CoV-2.**

EPIC-CROWN-2 TO ACCELERATE THE CLINICAL PHASE

The EPIC-CROWN-2 project, driven by Fab'entech as part of a consortium of 5 partners[1], was selected by the European Commission in response to the first call for HERA projects to combat SARS-Cov-2 and its variants. With global funding of 9.2 million euros, the consortium is one of the 11 European projects selected. **Since the start of the Covid-19 pandemic, Fab'entech has drawn on its expertise and past experience in the field of infectious diseases to develop and produce a polyclonal antibody treatment against SARS-Cov-2 with high neutralising ability known as FABENCOV.** Targeting the treatment of at-risk patients with moderate to severe symptoms of respiratory distress, it has provided the preclinical demonstration of its efficacy against the main variants currently circulating.

The aim of the EPIC-CROWN-2 project is rapid assessment of the clinical benefits of FABENCOV in a multi-centre Phase II a/b study on 400 patients, conducted in four European countries. Moreover, additional studies conducted *in vitro* and *in vivo* **will make it possible to optimise the product's therapeutic indications** by documenting its neutralising ability on variants of interest and by evaluating the clinical biomarkers used to refine the target population.

VALUABLE EUROPEAN SUPPORT FOR FAB'ENTECH

FABENTECH

FAB'ENTECH

Release Summary

The EPIC-CROWN-2 project initiated by Fab'entech received funding of 9.2 million € from the European Commission to develop its treatment for COVID-19

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Figure 9 – "businesswire" article to FABENTECH (https://www.businesswire.com/)

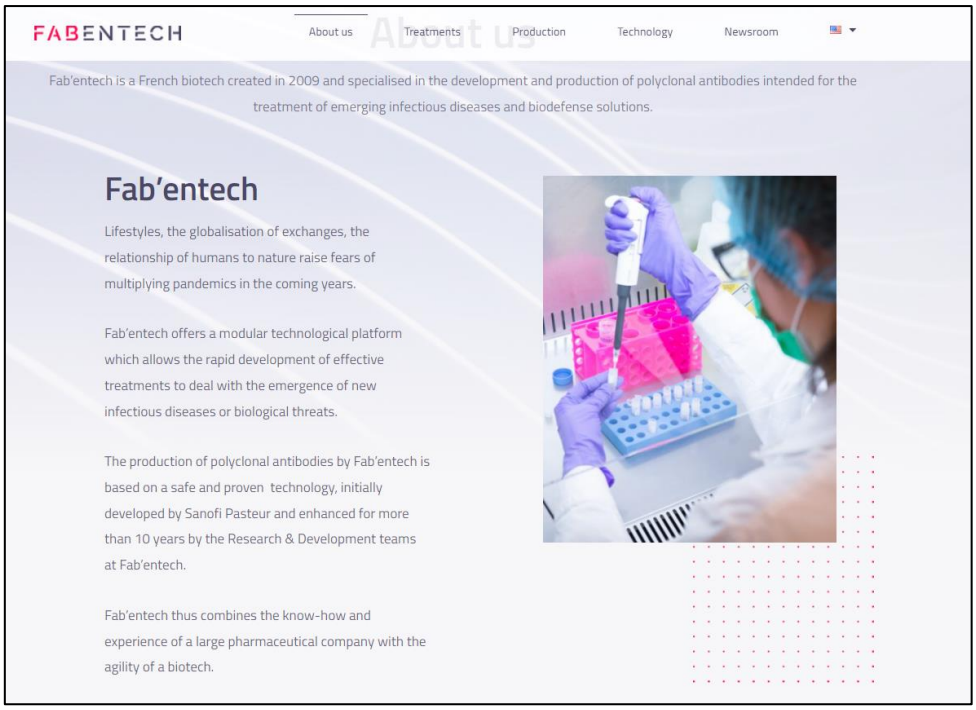

Figure 10 – Website FABENTECH (https://fabentech.fr/en/about-us/).

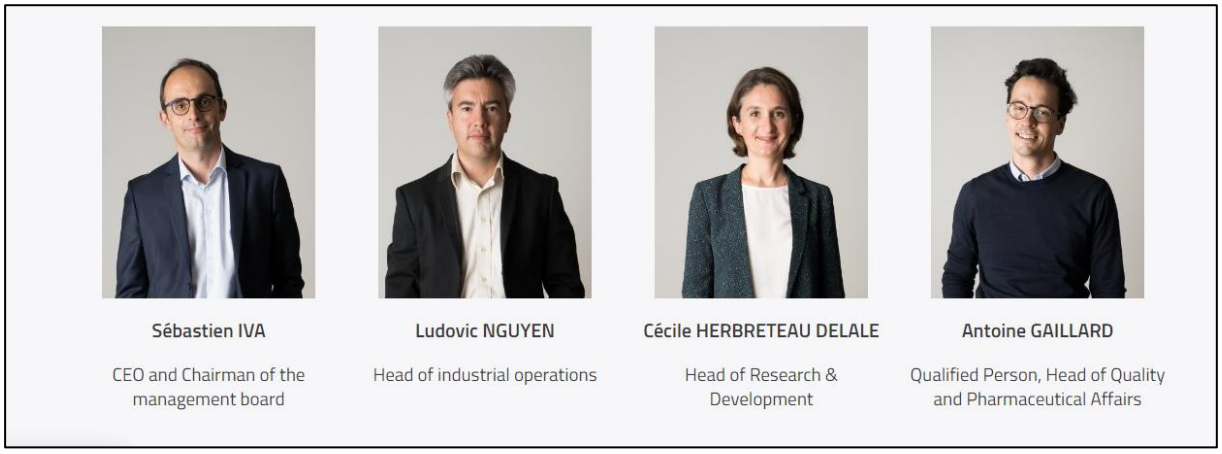

Figure 11 – Team FABENTECH.

3.4.2 Cooperation

While FX06 positively influences the healing process of the endothelium for mild to moderate cases, FABENCOV provides a powerful neutralizing immune response with polyclonal antibodies to neutralize the SARS-CoV-2 virus, especially for moderate to severe symptoms and respiratory distress. Both drugs therefore target different therapies and it is conceivable that the drugs may be administered in combination in the future. Therefore, a cooperation might be possible.

3.5 MetrioPharm AG – iMPact

3.5.1 Project Information

The iMPact project conducted by MetrioPharm AG (Switzerland) describes a novel, orally available immune modulator MP1032 with anti-SARS-CoV-2 and anti-cytokine activity. The consortium consists of four partners from Austria, Switzerland, Germany and the Netherlands. The project includes conducting a Phase II clinical trial with MP1032 and a preclinical assessment of the effect of the drug on mutant variants of SARS-CoV-2. MP1032 has so far demonstrated anti-inflammatory and anti-infective effects and a promising safety profile in preclinical and clinical studies. Now, MetrioPharm is conducting Phase II clinical trial in COVID-19 patients. Further information on the iMPact project can be found on their website (https://www.metriopharm.com/en/) (see also figure 11 and 12).

3.5.2 Cooperation

While FX06 positively influences the healing process of the endothelium for mild to moderate cases, MP1032 provides a powerful immune response to neutralize the SARS-CoV-2 virus. MP1032 is targeting a key mechanism of all inflammatory diseases: Oxidative stress. It is an orally available, self-regulating ROS (reactive oxygen species) scavenger: It is a small molecule drug with a strong antioxidant effect that is selectively activated only in cells with excessive ROS levels, i.e. cells with oxidative stress. In healthy, non-inflamed cells and tissues, the drug remains inactive. Both drugs i.e. FX06 and MP1032 are targeting the host response i.e. they do not directly interact with the virus. It is possible though, that these both drugs might act synergistically. Therefore, a collaboration might be possible in the future.

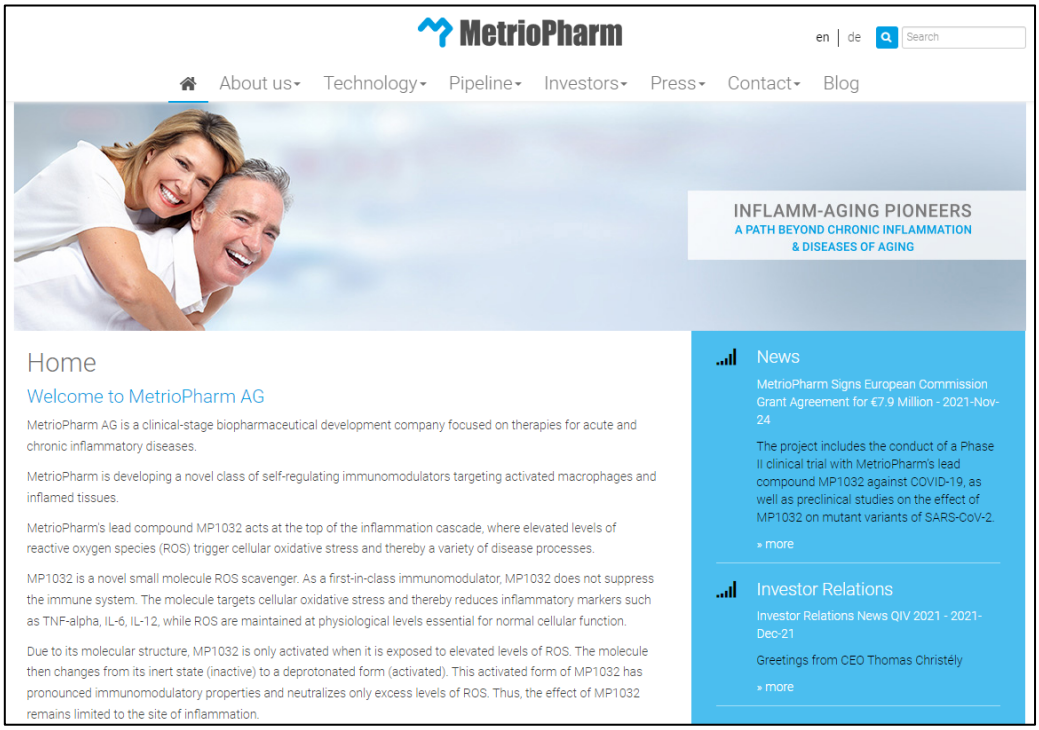

Figure 11 - Website MetrioPharm (https://www.metriopharm.com/en/)

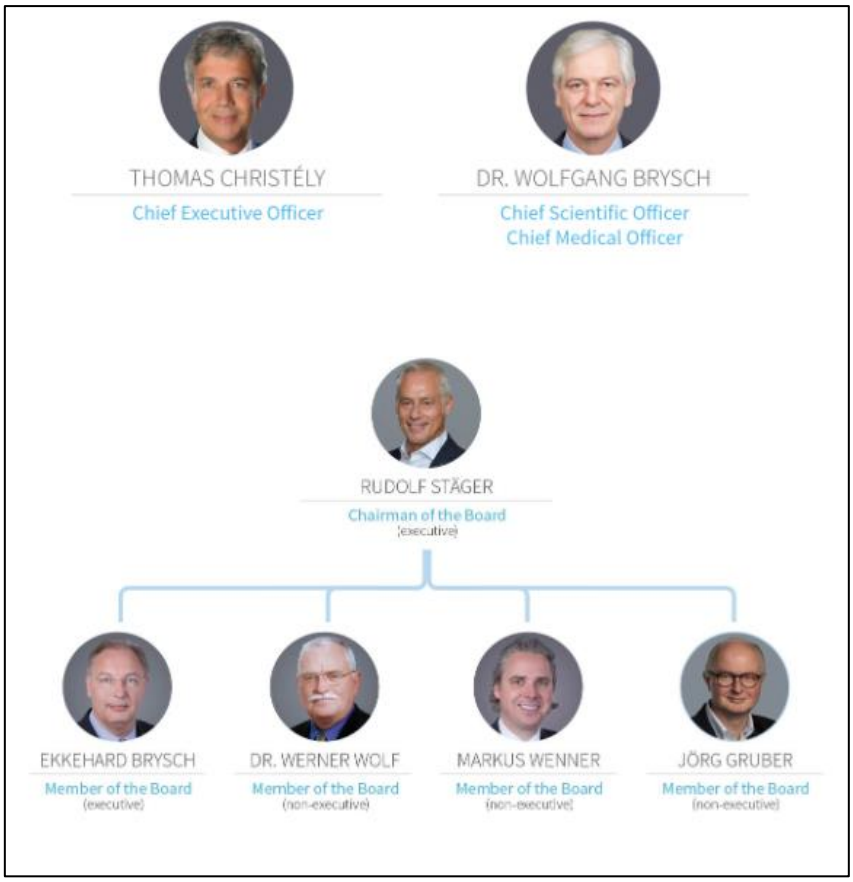

Figure 12 - Team of MetrioPharm.

4 Other Initiatives

All COVend partners have extensive experience in collaborative projects at both national and European levels. The following research and innovation activities support the COVend concept and will be relevant for the development and success of the project.

4.1 RECOVER

All COVend partners are committed to establish a closer collaboration with RECOVER, which aims to understand the COVID-19 pandemic through clinical research via studies on primary care, hospital care, clinical biology, epidemiology and modelling and the social sciences. Considering their research on milder COVID-19, their long involvement in emerging epidemics and their close cooperation with EU-RESPONSE, all COVend partners will facilitate knowledge transfer and look for peer feedback during the course of the project.

4.2 RECOVERY

F4 Pharma GmbH (Dr. Petra Wuelfroth), sponsor of COVend, has been closely following the progress of RECOVERY, a clinical trial being conducted by researchers at the University of Oxford, that aims to compare several different treatments that may be useful for patients with COVID-19. F4 already applied

for inclusion in the RECOVERY trial. COVend will benefit from their trial protocol and experience to help in developing its own clinical trial.

4.3 CARE

GUF (Prof. Maria Vehreschild) employ their expertise on the detection and characterisation of antiviral drugs for coronaviruses and other viruses to CARE, the largest European research initiative aiming to accelerate development and use of effective therapies for COVID-19 patients worldwide. GUF's involvement in the screening of potential drug candidates, as well as in the coordination of clinical trials, supports COVend to generate a hopefully transformative therapy regiment.

5 Summary and Outlook

The demand for therapies will remain urgent, including those deployed early in infection to stop replication of the virus and degradation of the patients' health. All the above projects and leading initiatives aspire for the same outcome: to provide a more significant offer of therapies for those suffering from COVID-19 symptoms. It is currently being considered whether a direct approach to the various project partners would make sense at this stage since that is currently a plan from HaDEA to facilitate the network on behalf of all consortia. Nevertheless, all COVend partners are willing to follow-up on the developments from all other relevant initiatives and is open to establish synergies