COVend

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

https://covend-project.eu/

DURATION
01.08.2021 – 31.07.2024

BUDGET
9.9 million euro

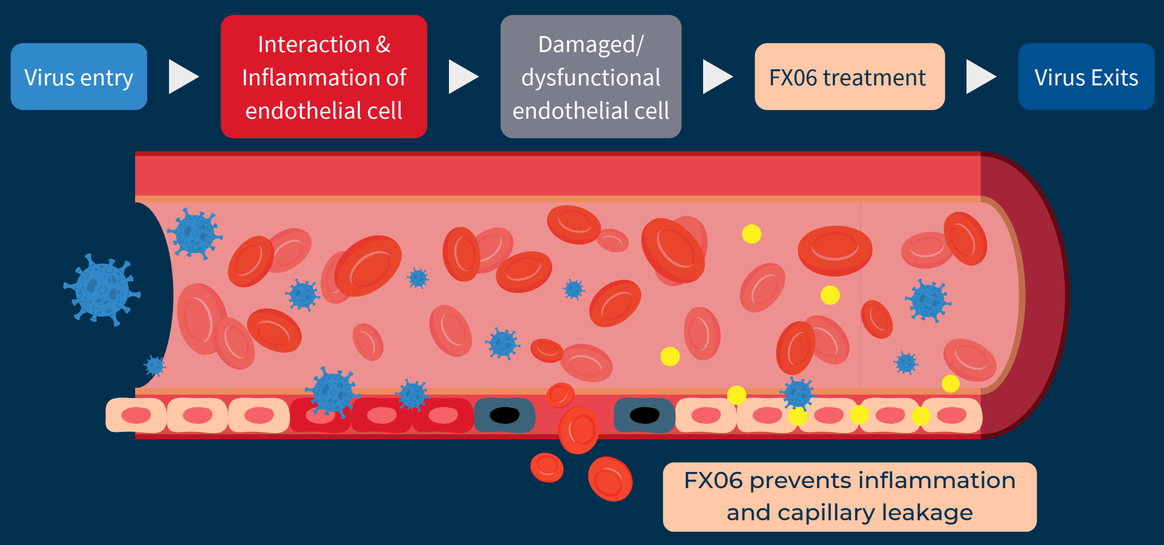
CALL TOPIC
HORIZON-HLTH-2021-CORONA

COORDINATOR
Goethe University Frankfurt, Germany

FX06 - innovative compound against capillary leak

FX06 competes with fibrin to reduce plasma leakage into tissue

Based on animal models, FX06 has considerable therapeutic potential for all diseases and pathological conditions associated with increased vascular permeability (Gröger *et al*. **2009** *PLoS ONE*, Bergt *et al*. **2016** *Crit Care Med*). FX06 binds to vascular endothelial (VE)-cadherin, preventing the transmigration of leukocytes.



Safety and efficacy evaluated in clinical studies

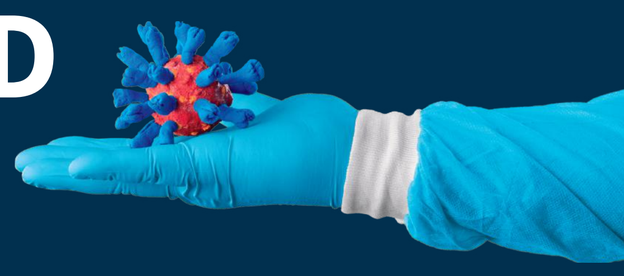
Severe infection

In a case study with an Ebola patient, FX06 administration led to a substantial improvement of vascular leak syndrome and respiratory parameters (Wolf *et al*. **2015** *The Lancet*).
In two German tertiary care university hospitals, six COVID-19 patients who suffered from moderate to severe ARDS at ICU admission were treated with FX06 as part of an elective rescue treatment of seriously ill COVID-19 patients (Adam *et al*. **2020** *Crit Care*). In the first three days after the start of FX06 administration, the mean oxygenation ratio improved, returned to baseline and then increased steadily thereafter from the seventh day.

Reperfusion injury

In a phase II study with 234 patients suffering from acute myocardial infarction, the therapy with FX06 showed a significant reduction of the necrosis zone 5 days after the event, evaluated by MRI. Patients treated with FX06 also showed a trend towards improvement of a combined clinical endpoint of mortality and any cardiac event (Atar *et al*. **2009** *J Am Coll Cardiol*).

THE COVEND PROJECT



- EU-wide, multicentre, placebo-controlled, double-blinded, parallel, randomized (2:1), phase II clinical study IXION to evaluate the efficiency of the FX06 endothelium-protective peptide.
- Multi-Omics of patient-derived samples to study COVID-19 pathogenesis and the influence of FX06.
- Quantitative assessment of the potential endothelium-protective effect of FX06 *in vitro*.
- AI-based open-source software for data analysis, clinical decision-making, and personalised treatment planning.
- Health-economic modelling to evaluate the socio-economic benefits and cost-effectiveness of the new therapy.

Research

- IXION phase II trial.
- Immuno-biomarker profiling.
- Endothelial cells assessment.

Development

- Drug production.
- AI decision support models.
- Personalised medication.

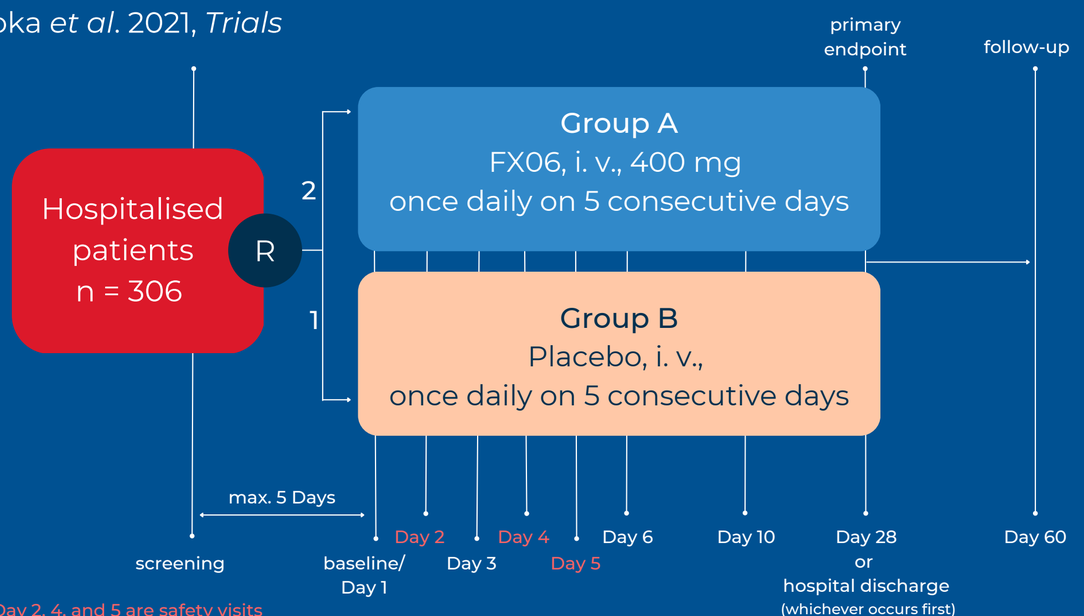
Outreach

- FX06 therapy.
- AI-based tools for healthcare workers.
- Clinical guidelines.

IXION Clinical Trial

An interventional study in nine European clinical centers

Kloka *et al*. 2021, *Trials*



Day 2, 4, and 5 are safety visits (assessment and documentation of safety endpoints)
FU can be performed as a phone call

"Having cured a patient with Ebola, it was clear to me that FX06 could also be beneficial against COVID-19."

Professor Kai Zacharowski, MD PhD ML FRCA, FESAIC
Ambassador & Immediate President of the European Society of Anaesthesiology & Intensive Care (ESAIC)
COVend Project Coordinator

COVend Partners

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accelopment takes you further
F4 Pharma
ESAIC European Society of Anaesthesiology and Intensive Care
Fraunhofer ITMP
umcg
Tampere University
MiDA Medical Intelligent Data Analytics
UCD DUBLIN
CHUC Centro Hospitalar e Universitário de Coimbra
Lietuvos sveikatos mokslų universiteto ligoninė Kauno klinikos
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Biomarker and AI-supported FX06 therapy to prevent the progression from mild and moderate to severe stages of COVID-19

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2 - University of Groningen, University Medical Center, Groningen, The Netherlands
3 - Goethe University, University Clinics, Frankfurt/M, Germany

FX06 therapy against capillary leak- from life science to market access

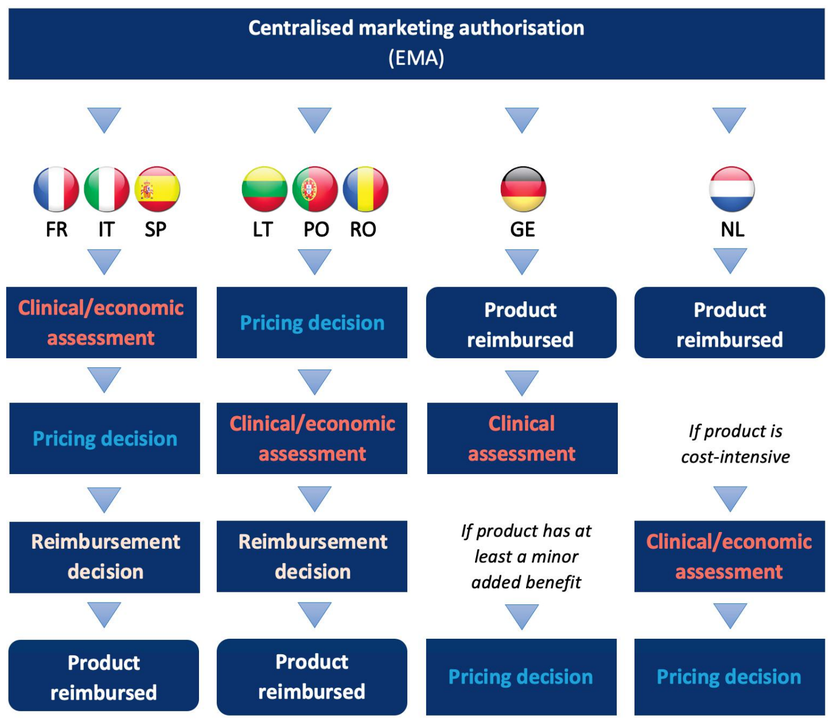
COVend aims to provide advanced therapy for capillary leak. The evidence from the clinical trial IXION is supported by sophisticated cellular and systems biology. Market access is facilitated by an extensive health-economic assessment.

Clazinus Veijer
Universitair Medisch Centrum Groningen

Health-economic modeling facilitates market access and reimbursement decisions for FX06 therapies

A flexible model will accommodate health economic analysis of FX06 in the context of various capillary leak disorders and country-specific policies

The sequence of regulatory steps and the assessment criteria in the reimbursement process varies across the countries that take part in the IXION trial. After a reimbursement decision has been made, the actual use and funding of inpatient medicines are in most countries dependent on a positive assessment by individual hospitals. A descriptive analysis of both national metho-dological guidelines for the conduct of health-economic evaluations as well as potential barriers and facilitators to the uptake of FX06 as a hospital drug addressed the need for a flexible health economic model. Technical guidance depends on a country's political and economic context, and end-users should be able to adjust the model to the context of a country's healthcare system (i.e. relevant comparators, clinical pathway, productivity loss calculation, etc.) to assess the system-wide cost-utility and hospital-specific budget impact of FX06.



Artificial Intelligence-supported therapy

Software for various clinical applications

AI-based automated characterisation of the study cohort using advanced unsupervised clustering methods will integrate a wide variety of data sources will such as Omics, vital signs, and open registry data.
A directed supervised approach will be used to train specific machine learning models that will provide new insights into patient properties and consider the time dynamics of the patient state to optimise and personalise treatment planning.

Quantitative biomarker analysis

Omics-based COVID-19 and therapy profiling

OLINK™ technology
Affinity-based, PCR-coupled, multiplexed high-throughout proteomics.

Selective and sensitive LC-MS/MS
Lipid mediators in blood plasma.

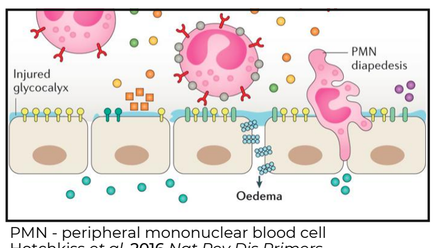
MxP® Quant 500 Assay, FIA-MS/MS, and LC-MS/MS
Small molecules, lipids, hexases to investigate metabolic pathways.

Proteomics, lipidomics, and metabolomics of patient-derived blood samples will provide a profound understanding of the interplay between the systemic inflammation of the endothelium caused by SARS-CoV-2 infection and the – also systemic – action mode of FX06.
Newly identified effector molecules will be studied *in vitro* and profiling data will be used to train AI for clinical application.
Multi-Omics revealed parts of the molecular signature of COVID-19 and the host immune response and were thus suggested for prognostic applications and drug target discovery (Li et al. 2021, Su et al. 2021).

Zhiran Wang
Vadim Zhernovkov
Systems Biology Ireland
University College Dublin

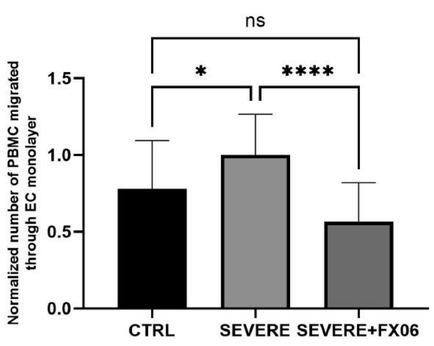
FX06 alleviates hyperinflammation and capillary leak

COVID-19-triggered transendothelial migration of immune cells from the blood is suppressed by FX06 *in vitro*



PMN - peripheral mononuclear blood cell
Hotchkiss *et al.* 2016 *Nat Rev Dis Primers*

Cytokines released during COVID-19 promote the disintegration of adherence junctions in the endothelial cell layer, the recruitment, and the transendothelial migration (TEM) of peripheral blood mononuclear cells (PBMCs).



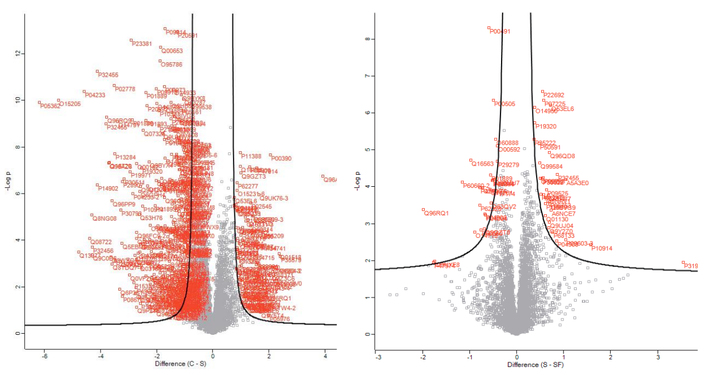
At computer-controlled laminar flow, we can mimic the shear stress conditions present in capillaries. After 24 h incubation with COVID-19-triggered cytokines (SEVERE), TEM of isolated PBMCs through a monolayer of human lung microvessel endothelial cells (HULEC-5a) is enhanced (*p = 0.0197). Pre-incubation of the ECs with FX06 for 2 h (SEVERE+FX06) can restore the non-inflammatory state (CTRL) and significantly reduce TEM (****p < 0.0001).

FX06 alters the protein expression pattern of ECs after stimulation with COVID-19-triggered cytokines

The cocktail of COVID-19-induced cytokines alters the expression of 456 proteins in ECs. Compared to this hyper-inflammatory state, 25 proteins are up- and 31 are down-regulated upon FX06 treatment, including Angiopoetin-related protein 4 (Q9BY76), which is known to reduce vascular leakage.

HULEC-5a, 24 h, COVID-19 cytokines compared to CTRL

following 6 h FX06 treatment, compared to non-treated cytokine-stimulated ECs



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