Project No. 101045956
Biomarker and AI-supported FX06 therapy to prevent progression from mild and moderate to severe stages of COVID-19

Deliverable 3.5

Report on first and last patient included

WP 3 – Management and implementation of therapeutic clinical trial

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Revision history

Date	Authors	Revision
09.05.2025	Sarah Steffens, Dr. Anita Bulczak-Schadendorf (F-ITMP)	Draft version
14.05.2025	Julia Dowell, Sylvia Daamen (ESAIC)	First revision
16.05.2025	Dr. Tanja Roßmanith (F-ITMP)	Final version

Contents

Partner short names

GUF	Johann Wolfgang Goethe Universität Frankfurt am Main
accelCH	accelopment Schweiz AG
ESAIC	European Society of Anaesthesiology and Intensive Care
Fraunhofer	Fraunhofer Institute for Translational Medicine and Pharmacology ITMP
F4	F4 Pharma GmbH
TAU	Tampereen Korkeakoulusaatio SR
UCD	University College Dublin
UMCG	Universitair Medisch Centrum Groningen
MiDA	Medical Intelligent Data Analytics GmbH
KC	Lietuvos Sveikatos Mokslu Universiteto Ligonine Kauno Klinikos
ICS-HUB	Hospital Universitari de Bellvitge
UMFCD	Universitatea de Medicina si Farmacie Carol Davila din Bucuresti
APHP	Assistance Publique – Hôpitaux de Paris

Abbreviations

ARDS	Acute Respiratory Distress Syndrome
CRA	Clinical Research Associate
CTIS	EU Clinical Trials Information System
D	Deliverable
DSMB	Data Safety Monitoring Board
EC	European Commission
EU	European Union
FPFV	First Patient First Visit
HEU	Horizon Europe
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier (IMPD)
LPFV	Last Patient First Visit
M	Month
MS	Milestone
PI	Principal Investigator

Executive Summary

Work Package 3 (WP3) "Management and implementation of therapeutic clinical trial" of the COVend project focuses on testing the therapeutic candidate, FX06. For scientific applications, a multicentric clinical study was conducted in five European countries to provide data regarding the safety and efficacy of FX06 in the treatment of mild/moderate Acute Respiratory Distress Syndrome (ARDS). To fulfill this goal, WP3 is divided into seven tasks.

- Task 3.1 – Preparation of study material;
- Task 3.2 – Site selection and collection of qualification;
- Task 3.3 – Submission to IRB and feedback of regulatory authorities;
- Task 3.4 – Set-up and maintain electronical data capture system (eCRF);
- Task 3.5 – Set-up and coordinate sites during study;
- Task 3.6 – Closing of study sites, data cleaning and data base closure;
- Task 3.7 – Data analysis and reporting.

After the basic requirements for conducting the clinical trial have been met (such as regulatory approvals, programming of the eCRF, contracting and training of clinical sites), this deliverable introduces the starting point of data collection (FPFV: first patient first visit) by enrolment of patients and the recruitment end (LPFV: last patient first visit) in the clinical trial.

Purpose and scope of the deliverable

The main purpose of WP3 is to gather the clinical data that form the basis for interdisciplinary analyses by the consortium partners in the COVend project. Deliverable 3.5 describes the pivotal step of patient enrolment in the clinical trial which lays the foundation for subsequent working tasks and analyses which are part of the COVend project.

Outcome

The first patient was recruited for the IXION 2.0 trial on 01 March 2024 (First Patient First Visit, FPFV) and recruitment was ended on 20 December 2024, with Last Patient First Visit (LPFV) taking place on 15 November 2024. In total, 19 ARDS patients were enrolled in 6 clinical sites in 5 European countries. 18 of these patients were randomised, while one was a ‘Screening Failure’ and could not be included into the study for randomisation.

The rate of patient recruitment varied over the months (seasonal fluctuation of infectious diseases) and clinical sites (all sites facing similar recruitment challenges).

Supporting measures were taken, in particular extending the project and the recruitment phase to include the autumn/winter period in which more ARDS patients were expected due to higher incidence of pulmonary infections and COVID-19 disease.

However, the planned recruitment target of 30-40 patients for IXION 2.0 could not be met.

1 Introduction

The COVend project was set up at a time when the COVID-19 pandemic was a global crisis, and the IXION study initially aimed to investigate the potential of FX06 to prevent disease progression in hospitalised non-intubated COVID-19 patients. The multicentric clinical trial with 9 clinical sites in 8 European countries was set up due to extensive collaboration of multiple parties. Besides the tasks for WP3, listed in the Executive Summary above, the intensive involvement of other work packages and external partners (such as central pharmacy, central laboratory, DSMB, CRAs) was required. This joint effort meant the following was achieved:

- design of study documents
- selection and contracting of clinical sites
- submission of study documents to the regulatory authorities (RA) and independent review boards (IRB) of all participating countries
- set-up and programming of a data entry system (electronic Case Report Form, eCRF)
- manufacturing, provision and distribution of the investigational medicinal product (IMP)
- preparation and distribution of study material (e.g. laboratory, documentation)
- training of all parties involved (e.g. site staff, CRAs).

After these tasks had been completed and all regulatory requirements fulfilled, recruitment for the trial could start in February 2022. However, by this time, the pandemic had significantly eased and only isolated COVID-19 cases required hospital care and patients with moderate to severe COVID-19 (the target patient group) were usually no longer hospitalised. This means that there were very few patients eligible for the trial.

Further obstacles to the start of recruitment included necessary changes to the Investigational Medicinal Product Dossier (IMPD) for the second batch of IMP due to some minor impurities. This required for a substantial amendment to be submitted to the competent authorities in all countries involved.

1.1 Change from IXION to IXION 2.0

Due to these circumstances, particularly the insufficient number of patients meeting the inclusion criteria, no patients could be included in the IXION trial until July 2023.

Given the decrease in hospitalized patients with moderate to severe COVID-19 disease, the consortium discussed at length a change of indication for the trial. A new strategy was developed to broaden the patient population and includer the indication of ARDS. It was agreed investigate the efficacy and safety of FX06 in ARDS by enrolling patients with mild to moderate ARDS with COVID-19 or other disease aetiology (Figure 1). This updated trial would be called IXION 2.0.

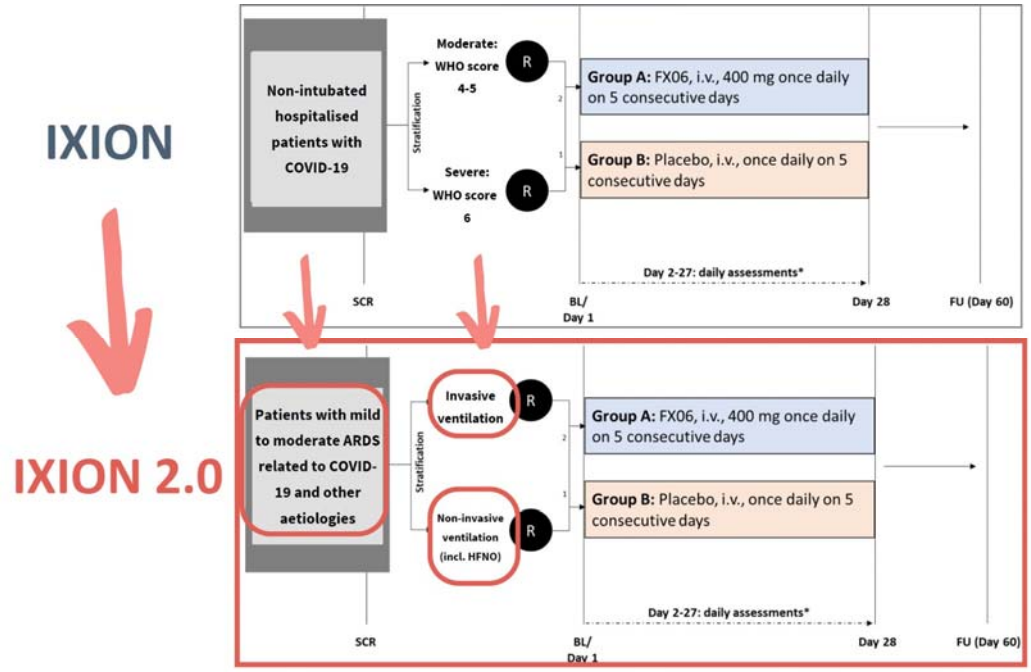

Figure 1: Flowchart of study design – IXION compared to IXION 2.0

In order to implement the new strategy for the clinical trial including a different patient population, the COVend consortium had to re-evaluate the involvement of several clinical sites with regards to feasibility and interest in participating in the new strategy, the expected number of patients meeting the inclusion criteria and the time for regulatory approval. Five sites in five different European countries were selected to continue in the implementation of the amended trial IXION 2.0. In addition, a new site was added in Paris at no additional costs:

1. GUF: Frankfurt University Hospital, Frankfurt, Germany
2. KC: Lithuanian University of Health Sciences Hospital, Kaunas, Lithuania
3. ICS-HUB: University Hospital of Bellvitge IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain
4. UMFCD: Faculty of Medicine, Fundeni Clinical Institute, Bucharest, Romania
5. APHP: St Antoine Hospital, Paris, France
6. APHP: Georges-Pompidou Hospital, Paris, France

All sites provided an expected number of patients meeting with the amended inclusion criteria of IXION 2.0. Since the numbers of ARDS cases exhibit seasonal fluctuations with a peak number expected in autumn and winter time, the feedback from several sites included that the recruitment rate will be highly dependent on a quick recruitment start.

Therefore, all efforts were made to obtain the regulatory approvals in the selected countries to be able to enroll the first ARDS patient with COVID-19 or other disease aetiology in at the end of October 2023.

Due to the change in patient population, recruitment in some sites moved from infectious disease departments to critical care, leading to changes in principal investigators (PI) and requiring new study teams, contracts, and site updates.

The new strategy for the ARDS study design (including a project extension until end of 2024) was presented to and approved by the consortium partners on 25 July 2023. This meant that the new protocol for IXION 2.0 could be finalised and include an extended recruitment phase until July 2024.

The substantial amendment for the IXION 2.0 protocol entailed comprehensive administrative and management activities, such as:

- adaption of the patient documents (informed consent form for patient and legal representative, patient card and GP letter) and associated translations
- substantial amendment submission to ethics committee and competent authorities in all countries taking part in IXION 2.0
- insurance prolongation under new study design for selected sites
- expansion of pharmacy and DSMB resources
- creation and validation of new eCRF for new pre-defined subgroups and update of randomisation process
- distribution of new IMP kits to sites
- update of IMPD that needs to be approved by competent authority
- training of CRAs and site staff on new study design, eCRF version and respective documents
- New or amended contracts with sites due to the change in PI

The adapted final protocol was submitted to BfArM (The German Competent Authority) as a substantial amendment to the previous protocol and was approved without objections on 15 September 2023. The ethical and competent authorities' approvals took longer in the other countries, and some involved numerous questions that had to be answered and required additional information. After the supply of a new IMP batch (the previous batch expired in November 2023) most clinical sites were ready to start recruiting by Spring 2024. Unfortunately, this meant that the most promising phase for the recruitment of infection-related ARDS patients (who are more present in autumn and winter seasons) was missed.

1.2 Further extension to recruitment period

Although the study started recruitment on 31 January 2024 (initially only Germany had all approval in place), recruitment was slow as mild ARDS is underdiagnosed and only few ARDS cases with advanced pathophysiology and comorbidities excluded by the study protocol were identified. To achieve the recruitment target (so that the collected data would lead to meaningful results), a further project prolongation was requested by the consortium partners and granted by the EU Officer. This meant that recruitment was extended until 25 November 2024. For continuous treatment, the shelf life of both the placebo and IMP were extended through an amendment of the ongoing stability study and relabeling and re-supply of IMP was carried out by the sponsor of the clinical trial (F4). To determine a

realistic target for the remaining recruitment period, a number of 50-90 patients was been deemed acceptable to gain convincing results for OMICs data (according to literature data). However, the clinical partners estimated a recruitment number of 30-40 patients which was calculated based on site-specific ARDS data from previous years.

As is shown in Figures 3 and 4 below, the patient recruitment rate increased during the colder months of the recruitment period, as was expected. Therefore, all efforts were made to recruit during the winter period. In order to continue recruitment after November 2024, the trial was transitioned to the EU's Clinical Trials Information System (CTIS) on 24 October 2024. Full regulatory approval for all countries was received on 09 December 2024 enabling another prolongation of the recruitment period until 20 December 2024.

As well as extending the recruitment time, the following strategies were put in place with the aim of increasing recruitment:

- to tackle the difficulties in primary diagnosis, several measures were implemented: clinical teams were regularly encouraged to intensify pre-screening activities to identify potential ARDS cases including:
    - looking in different wards
    - increased efforts to disseminate information about the study within clinical wards
    - raising awareness among healthcare professionals
    - posters and flyers were offered to all clinical sites for display to staff
    - and finally, training sessions for clinical teams were reiterated, with a focus on the eligibility criteria for the study.
- ESAIC, in collaboration with the Fraunhofer team and the chief investigator, distributed a newsletter biweekly to the clinical partners to update the clinical sites and to keep them motivated and informed about the study
- four online meetings were organised for clinicians to share their experiences and suggestions regarding recruitment
- email addresses and phone numbers for key contacts were provided to ensure that any eligibility questions can be answered as quickly as possible, including during evenings and weekends.
- all sites were continuously encouraged to keep track of potential patient numbers. Information provided by sites was recorded weekly in a study dashboard and pre-screening information was requested from sites on a bi-weekly basis.

2 IXION 2.0 recruitment figures

The planned recruitment target for the IXION 2.0 protocol was 263 ARDS patients, within the defined recruitment phase from Q4/2021 to Q2/2024. Although the recruitment period was extended, the target recruitment number in the protocol remained the same.

The first patient was enrolled on 01 March 2024 (FPFV). The last patient was included and randomised on 15 November 2024 (LPFV).

In total, 19 patients were enrolled in the study until end of recruitment on 20 December 2024. 18 of which were randomized, while one Screening Failure was not randomised due to worsening of a condition (septic shock) after the screening visit. Further patients were invited to participate but did not consent because they declined due to reservations about taking part in a clinical trial or because of language barriers.

The patient numbers are not evenly distributed across the clinical sites. The highest recruiting site was Frankfurt University Hospital in Germany (9 patients, including one Screening Failure) and unfortunately, in Romania no patient could be identified for study participation despite the site staff's best efforts (Figure 2).

Country	Site	Total number of patients randomised
Germany	049-001 GUF	8
Lithuania	370-001 KC	4
France	033-001 AP-HP: St Antoine	3
	033-002 AP-HP: George Pompidou	1
Spain	034-001 ICS-HUB	2
Romania	040-001 UMFCD	0
Total		**18**

Figure 2: Randomisations by site

Discussions during several recruitment calls with the sites revealed that different sites were facing the same hurdles for inclusion of patients: given the fact that mild to moderate ARDS is often not diagnosed as such on normal ward, most ARDS cases on intensive care showed severe progression, often accompanied by concomitant diseases that are excluded by protocol (advanced septic shock, advanced cardiac problems, advanced liver problems). The few mild to moderate ARDS cases identified often met exclusion criteria and in some cases patients or their representative refused the

participation on a clinical trial. To tackle these issues, the adaptation of the eligibility criteria was discussed, but no changes were deemed as effective.

The monthly distribution of patient numbers shows the expected trend of an enhanced recruitment potential during the colder months of the year (Figure 3). While during March, October and November 3-4 patients each were enrolled, only 1-2 patients per month could be included during spring and summer period. In September and December no patients were found.

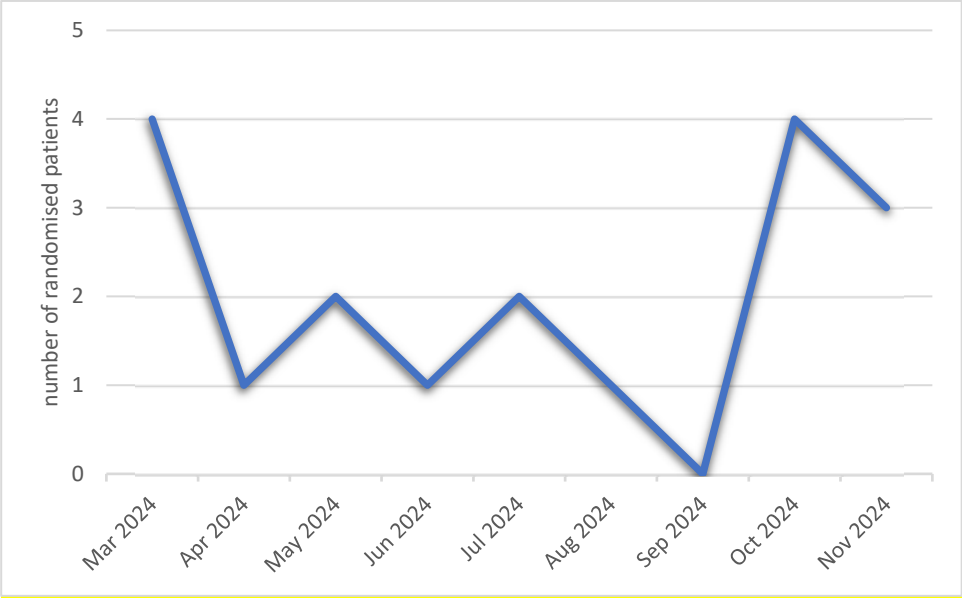

Figure 3: Randomisations over time

The sharp increase of patient numbers during the colder months of the recruitment period gives a hint that extending the recruitment phase further into the winter period would have affected the total number of patients positively (Figure 4).

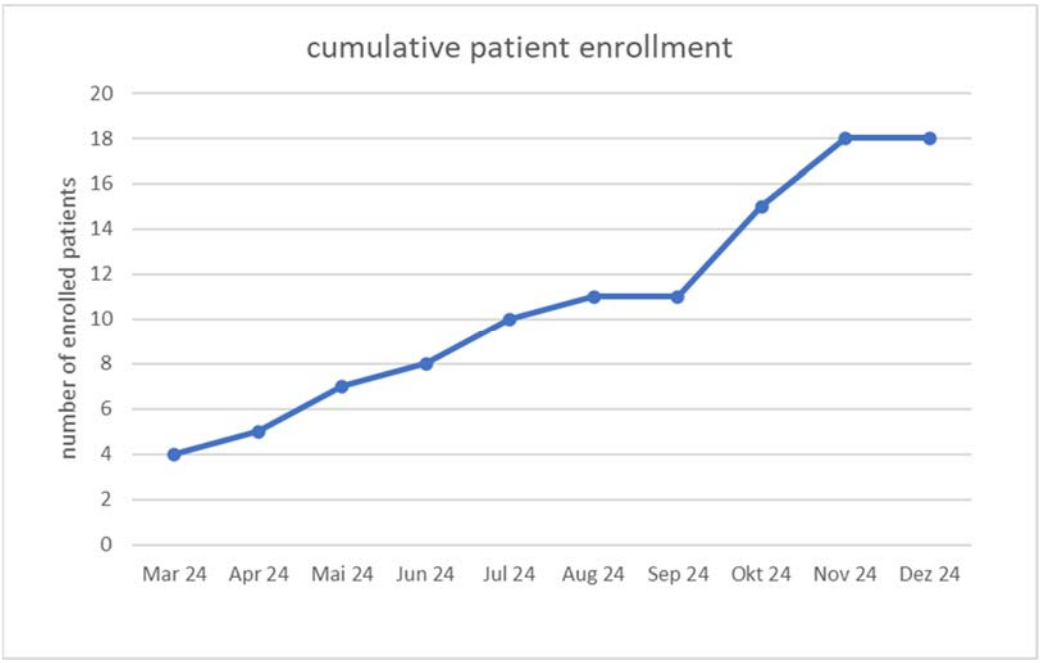

Figure 4: Positive effect of recruitment extension on patient enrollment

Unfortunately, no patients could be enrolled within the additional timeframe in December and following the two project extensions, no further extension was suitable due to financial limitations of the COVend project.

3 Outlook

The data from the patients recruited into the trial will be entered in the eCRF and their visit assessments will be fully documented. The data undergoes regular monitoring to verify study integrity, ensure compliance with the protocol and regulations, and safeguard patient safety. Any discrepancies will be queried by the data management team, while medical data will be reviewed by an expert to ensure accuracy and reliability for the database lock.

Despite having less data available for analysis than initially planned, there is still potential for a visible effect on plasma protein levels. It is anticipated that the results of OMICs measurements will play a valuable role in identifying molecules or biomarkers that support the advancement of personalised decision support models.