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

Deliverable 3.6

Last patient last visit and data base closure

WP 3 – Management and implementation of therapeutic clinical trial

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Delivery date	28 May 2025
Dissemination level	PU - Public
Type	R - Document, report

Version 1.0

Funded by the European Union

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Revision history

Date	Authors	Revision
19.05.2025	Sarah Steffens, Dr. Anita Bulczak-Schadendorf (F-ITMP)	Draft version
21.05.2025	Julia Dowell, Shruthi Madappa, Sylvia Daamen (ESAIC)	First revision
28.05.2025	Dr. Tanja Roßmanith (F-ITMP)	Final version

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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
DM	Data Management
DO	Drop Out
DRBM	Data Review Board Meeting
DSMB	Data Safety Monitoring Board
EC	European Commission
eCRF	Electronic Case Report Form
EU	European Union
FPFV	First Patient First Visit
IMP	Investigational Medicinal Product
LPFV	Last Patient First Visit
LPLV	Last Patient Last Visit
MedDRA	Medical Dictionary for Regulatory Activities dictionary
PI	Principal Investigator
PM	Project Management
PVG	Pharmacovigilance
SF	Screening Failure
STAT	Statistics/Statistician
SUSAR	Suspected Unexpected Serious Adverse Reaction
WHO-DD	World Health Organisation Drug Dictionary
WP	Work Package

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.

Following the description of the recruitment outcomes in Deliverable 3.5, Deliverable 3.6 summarises the processes that take place after completion of all patient study visits in order to ensure validated data for final analyses by STAT, WP6 and WP7.

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 3.6 introduces the structure of the collected clinical data and the crucial steps of data cleaning and data base closure in preparation of the statistical analysis and delivery to the work package partners.

Outcome

Last Patient Last Visit (LPLV) of the IXION 2.0 study took place on 13 January 2025, having enrolled 19 patients into the study, of which 18 had been randomised. After comprehensive data cleaning, medical coding and data review, the study database was hard locked on 31 March 2025. During the blinded Data Review Board Meeting (DRBM) on 21 March 2025, two patients were excluded from the per protocol analysis set due to major protocol deviations while all 18 patients were assigned to the full analysis set and safety analysis set. After unblinding of the treatment, the unblinded data listings were delivered to the statistician as well as to the work package partners (WP6, WP7) for analyses.

1 Introduction

Valid clinical data sets form the basis of every clinical trial and the significance of results essentially depends on the quantity and quality of the data collected during the trial. While the statistical power is reached by a high sample size number, one tool to ensure the data integrity is comprehensive data cleaning. The process of data cleaning includes the identification and correction of errors and inconsistencies in datasets to improve data quality and hence to ensure accurate and reliable analysis.

In this report, the characteristics of the collected IXION 2.0 clinical data in terms of quantity and quality are described:

Data quantity
While the decrease in eligible COVID-19 patients due to the changing dynamics of the pandemic was the main reason for non-enrolment in the IXION trial, the underdiagnosis of mild to moderate ARDS was the main obstacle and reason for the low number of ARDS patients included in IXION 2.0.

Section 2 of this report summarises the structure of the clinical data of the 18 patients enrolled in the study.

Data quality
Data quality refers to the degree of accuracy, completeness, consistency and reliability of data which is essential for further analyses and meaningful results of a clinical trial. To ensure the generation of high-quality datasets, various tools can be applied in different phases of the clinical trial, such as validation (study design/set up), data monitoring and profiling (study conduct) and data cleaning (study conduct/data base closure).

Sections 3 and 4 of this report depict the processes and milestones of data base cleaning and data base closure to warrant the integrity and validity of data for later analyses. These include the assignment of the patients to analysis sets defined in the study protocol based on discussion and evaluation of protocol deviations during a Data Review Board Meeting (DRBM).

2 Last patient last visit (LPLV)

While the milestone First Patient First Visit (FPFV) represents the start of recruitment and hence the start of data acquisition, Last Patient Last Visit (LPLV) marks the point of completion for data collection in a clinical trial. On this date, the clinical sites have gathered all subject and visit data by completing the visit assessments (as described in the protocol), and ideally, documented all collected data in the eCRF.

IXION 2.0 recruitment started on 01 March 2024 with the first patient signing the informed consent form of the study (FPFV). The last patient was randomised into the trial on 15 November 2024 (Last Patient First Visit, LPFV). A total number of 18 patients were enrolled, randomised and treated with IMP, while one patient failed randomisation due to worsening of condition (septic shock) after the screening visit (Screening Failure, SF).

The last study visit (Last Patient Last Visit, LPLV) was performed on 13 January 2025.

12 of the 18 randomised patients completed all 30 patient visits (Table 1). 6 patients did not complete all study visits as scheduled: 4 of these patients died in the course of the study due to worsening of condition of the underlying disease (without relation to IMP) and 2 of these patients dropped out during follow-up visits (lost to follow-up at visit 25, withdrawal of consent at visit 11).

The protocol states that IMP must be administered daily for 5 consecutive days but 2 patients did not complete IMP administration until day 5 (due to SUSAR and withdrawal of consent).

Subject ID	Subject status	Participant eligible for randomisation?	IMP administration completed for the subject?	Subject completed study as scheduled?	Reason for early termination
033001001	Enrolled	Yes	Yes	Yes	
033001002	Enrolled	Yes	Yes	Yes	
033001003	Enrolled	Yes	No	Yes	
033002001	Enrolled	Yes	Yes	No	Death
034001001	Enrolled	Yes	No	No	Withdrawal of Consent
034001002	Enrolled	Yes	Yes	No	Death
049001001	Enrolled	Yes	Yes	Yes	
049001002	Enrolled	Yes	Yes	Yes	
049001003	Enrolled	Yes	Yes	No	Lost to follow-up
049001004	Enrolled	Yes	Yes	No	Death
049001005	Screening Failure	No	NA	No	Screening Failure
049001006	Enrolled	Yes	Yes	Yes	
049001007	Enrolled	Yes	Yes	Yes	
049001008	Enrolled	Yes	Yes	Yes	
049001009	Enrolled	Yes	Yes	Yes	
370001001	Enrolled	Yes	Yes	Yes	
370001002	Enrolled	Yes	Yes	No	Death
370001004	Enrolled	Yes	Yes	Yes	
370001005	Enrolled	Yes	Yes	Yes	

Table 1: IXION 2.0 patient status

In total, 18 SAEs were reported for 11 patients. 10 of these 18 events were reported for the four patients who died during the study. All SAEs were assessed by a second evaluator and monitored on a regular basis by the Data Safety Monitoring Board (DSMB) who confirmed to have no safety concerns linked to IMP treatment neither for the individual patients nor for the entire patient population. In France, one SUSAR (Suspected Unexpected Serious Adverse Reaction) was reported for a patient who was HIV-positive. The Principal Investigator (PI) and Coordinating Investigator did not think the patient needed to be unblinded, but when the data was unblinded at the end of study, it was learned that this patient was given FX06 treatment. The PI confirmed the SAE/SUSAR of this patient had the status 'recovered' 16 days after start of the event. However, as another HIV-positive patient at site showed a similar (but not serious) deterioration of disease after FX06 treatment, the DSMB recommended a more in-depth analysis for potential risk factors in HIV patients when they discussed the study data after database closure.

3 Data cleaning

As all the patient data is not entered in the eCRF on the date of the LPLV, which is common in clinical trials, the first step towards data cleaning and data base closure was the completion of data entry for all study visits into the eCRF by the site personnel.

To ensure data integrity and compliance with the study protocol, the CRAs performed comprehensive source data verification (SDV) of the documented eCRF data during regular monitoring visits. All collected data was cleaned by resolution of queries (by clinical site personnel), which had been posted and were followed-up by the CRAs or DM/PM. For several of the sites, the CRAs completed additional visits at the sites to ensure all data was correctly entered. Identified protocol deviations were recorded in a separate eCRF environment and documented in the monitoring visit report by the CRAs, and then reviewed by the PM. On 10 March 2025, the completeness and correctness of the recorded data was confirmed by all clinical sites via eCRF signature by the Principal Investigator (PI) (Table 2).

In parallel to the cleaning of eCRF data, the medical coding was conducted by the DM and reviewed by a medical expert. Medical coding aims to convert clinical data documented by the clinical site staff into standardised international medical terminology (universal alphanumeric codes) which is essential for statistical analysis. Adverse events (AE), serious adverse events (SAE), medical history conditions, concomitant diseases, COVID vaccination and ARDS cause were coded according to MedDRA (Medical Dictionary for Regulatory Activities dictionary) while for concomitant medication and procedures were transformed into WHO drug dictionary terms (WHO-DD, World Health Organisation Drug Dictionary).

For compliance with pharmacovigilance (PVG) standards, the DM performed a final SAE reconciliation to ensure consistency between the clinical safety data (recorded in the eCRF) and the information in the PVG data base (SecuTrial safety data base). Discrepancies identified were corrected in the respective data base (eCRF/SecuTrial safety data base) by DM/PM.

Milestone	Date completed
LPFV	15-Nov-2024
Recruitment stop	20-Dec-2024
LPLV	**13-Jan-2025**
Data entry complete	10-Mar-2025
Last query resolved	10-Mar-2025
SDV complete	10-Mar-2025
PI signature complete	10-Mar-2025
Coding listings signed	18-Mar-2025
Soft Lock	20-Mar-2025
DRBM	21-Mar-2025
Final SAE reconciliation	26-Mar-2025
Hard lock	**31-Mar-2025**
Shipping of central lab samples	Apr-2025
Unblinding and delivery of datasets to STAT	04-Apr-2025
Start of site closure (FR, ES, DE, LIT)	22-Apr-2025
Delivery of datasets to WP6	19-May-2025
Delivery of datasets to WP7	19-May-2025
Delivery of OMICs datasets to WP6	TBC
Analysis and reporting	TBC

Table 2: IXION 2.0 Milestones for project closure

After completion of all data cleaning tasks, the Soft Lock of the eCRF data base took place on 20 March 2025.

4 Data base closure

Based on first data insights following the data base Soft Lock, the quality and relevance of the data collected is evaluated during a Data Review Board Meeting (DRBM). The main objective of the meeting is to allocate the patient data into the analysis sets defined by the study protocol. In particular, based on the reported findings, all protocol deviations were discussed among Sponsor, Coordinating Investigator, PM, DM and the statistician (STAT) to assess their impact and meet a joint decision on the assignment of the subject data to the analysis sets. The analysis sets are explained below:

- **Safety analysis set**: All randomised subjects with at least one IMP dose administered.

- **Full analysis set**: All subjects with at least one IMP dose administered who had a baseline and one post-baseline assessment of their disease state based on the ventilation status.

- **Per protocol analysis set**: Subset of full analysis set excluding those patients with major protocol deviations occurring up to day 28.

All protocol deviations, both manual (reported by CRA/PM) and programmatic (automatically detected and listed from data in eCRF after data entry), were reviewed and assessed with regards to their impact on primary/secondary analyses leading to the following results:

- **Safety analysis set**: All 18 subjects randomised in the study are part of the safety analysis set.

- **Full analysis set**: All 18 subjects randomised in the study are part of the full analysis set.

- **Per protocol analysis set**: 16 out of the 18 subjects randomised in the study are part of the per protocol analysis set. Two patients are excluded due to important protocol deviations and their interference with the primary analysis (violation of inclusion criterion 1).

As well as from the evaluation by the Data Review Board, the eCRF data were inspected by a medical expert for consistency from a medical perspective. The medical review focussed on the key data points of the study protocol: eligibility data (inclusion/exclusion criteria), safety listings (AE/SAE), ventilation status (primary endpoint) and concomitant medication. Apart from the eligibility issues discussed during the DRBM, no major discrepancies were found.

Subsequently, the data base hard lock was performed on 31 March 2025.

Following the hard lock, the sponsor initiated the treatment unblinding and the data sets prepared by the DM were shared with the statistician for analyses.
The delivery of the unblinded data sets to work packages 6 (Decision support models) and 7 (Socio-economic impact and cost effectiveness analyses (HTA)) was slightly delayed due to delays in finalising of a data transfer agreements.

In parallel to data cleaning, the patient's blood plasma samples were prepared for shipment from the clinical sites to the central laboratory for molecular phenotyping via OLINK and OMICs measurements. For reconciliation of the central laboratory data the subject IDs and visit numbers of all samples collected were shared with the DM. The results from the measurements will be delivered with the work package 6 partners for analysis towards the development of personalised decision support models.

The sites of the clinical partners were closed by CRAs, in close communication with the PMs. The close out visits (COV) took place in April and May 2025, with the purpose to close pending issues, obtain essential study documents and prepare the site's study documents for archiving.

5 Outlook

The successful completion of the last patient visit and subsequent database closure marks a pivotal step in this clinical trial. With all data now secured, the unblinded datasets will undergo statistical analysis, with a synoptic study report prepared to summarize the key findings, including the statistical outcomes of primary and key secondary efficacy objectives and safety analysis.

Although the dataset is smaller than originally planned, there remains potential for observable effects on plasma protein levels. The results of OMICs measurements are expected to provide valuable insights, aiding in the identification of molecules or biomarkers that contribute to the development of personalised decision support models.