Decision on Optimal Combinatorial Therapies in IMIDS using Systems Approaches

DocTIS

Deliverable D8.1

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VERSION	DESCRIPTION OF CHANGE
V1.0	

1. INTRODUCTION

1.1 OBJECTIVES OF WORK OF WP8:

1) Provide proof-of-principle validation of the efficacy of the combinatorial therapy identified by WP6 in patients with different IMIDs
2) Provide preliminary safety and tolerability data on the selected combination therapy

1.2 SCHEDULE AND DELIVERABLES

D8.1 Midterm recruitment report
Overview of recruited subjects by study site, potential recruiting problems and, if applicable, a detailed description of implemented and planned measures to compensate delays in the study subject recruitment.

D8.2 Report on status of posting results
Report on the status of posting results in the study registry, including timelines when final posting of results is scheduled after end of funding period.

2. WORK COMPLETED IN D10.1 AND 10.4

2.1 CLINICAL STUDY PROTOCOL

At the general assembly in Jan 2024, WP8 proposed and discussed several options of the clinical trial design. A Simon 2-stage adaptive basket trial assessing adding tocilizumab, an interleukin-6 inhibitor, to a tumour necrosis factor inhibitor (TNFi) in patients with rheumatoid or psoriatic arthritis was approved by the General Assembly in Apr 24. Treatment would last for 24 weeks, and the primary endpoint of the trial would be rate of remission at 24 weeks.

April-Jun 2024
Documents were prepared and submitted to Cardiff University to formally accept sponsorship. Documents including protocol, participant information sheet, consent form, risk assessment and monitoring plan were prepared for regulatory and ethics application. First drafts of these documents were submitted for review by sponsors, healthcare professionals including rheumatologist, nurses, patients and Centre for Trials Research internal review.
Sites and recruitment plan were drafted and discussed with the coordinating centre of DocTIS. Our initial plan was to open 5 sites in the UK and 5 sites in Spain who have agreed in principle to take part.

Jul-Sep 2024
Trials documents were revised at the end of September 2024 after comments were received and were submitted to sponsor and Centre for Trial Research for final approval before submission to UK Medicine and Healthcare products Regulatory Agency (MHRA) and national ethics committee.

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Statistical analysis plan, case report form and study database design were initiated and first draft completed. Biomarker sample collection and processing protocol, supply of study medication by pharmacy were drafted and completed,

Sep-Dec 2024
Review all study documents and prepared submission to MHRA and national ethic committee. Submission was made on 17 Oct 24 (deliverable 8.1.2) and responses received on 8 Nov 24. Responses and revision to study documents were prepared and resubmitted to MHRA and ethics completed on 21 Nov 24. Conditional approval by MHRA and national ethic committee was received on 17 Dec 24 (D10.4). However, the regulatory approval was contingent on the addition of a telephone follow up assessment, 60 days after treatment. Study was registered with the UK Clinical Study Registry, ISRCTN50666516.

Jan – Mar 25
Amended protocol and study documents were submitted to MHRA and ethics committee were submitted and approval received in Feb 25. The first Trial Management Group meeting was held in Feb 2025. Training documents for investigators and pharmacy were finalised. Site recruitment and contract discussion initiated.

Apr – Jun 25
EU regulatory and ethics application was submitted on April 1st, 2025, EU regulatory authority has raised minor queries requiring minor amendment to the protocol. Although this can be readily addressed, it has delayed in initiating the trial in Spain. CTIS approval is not expected until June/July 2025. However, this will allow sites in Spain to join the trial. Vall d'Hebron Research Institute will be coordinating centre and 2 sites have agreed to take part from Spain.

The Independent Data Monitoring Committee (IDMC) has met in May 2025, and approved the trial design, protocol and planned analyses. The IDMC charter has been signed.

2.2 Deliverable 8.1
Overview of recruited subjects by study site, potential recruiting problems and, if applicable, a detailed description of implemented and planned measures to compensate delays in the study subject recruitment.

The original plan was to recruit patients from 5 sites in the UK and 5 sites in Spain.
Due to the delay in needing to have amendments mandated by MHRA approved by ethics and MHRA. Contract negotiation, site initiation and recruitment has been delayed from March to June.

2.2.1 Current trial status in the UK:

- Number of patients recruited: 1 (Cardiff and Vale University Health Board)

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- Number of site active recruiting patients: 2 (Cardiff and Vale University Health Board, Aneurin Bevan University Health Board,)
- Contracts site and site initiation training pending: 2: (Swansea University Health Board and Brighton and East Sussex NHS Trust)
- Cwn Taf University Health Board moving forward with contract approval.

2.2.2 Current trial status in the Spain

EU regulatory and ethics application was submitted on April 1st, 2025, CTIS approval is not expected until June/July 2025. However, this will allow sites in Spain to join the trial. Vall d'Hebron Research Institute will be coordinating centre and 2 sites have agreed to take part from Spain.

2.2.3 Plan to compensate for delay

To mitigate the effect of regulatory delays, the number of sites will be increased in the UK.

Five more sites in the UK have been approached. These are:

- University Hospital of Lewisham – moving forward with approval
- University of Sheffield - Expression of Interest
- Portsmouth University Hospital NHS Trust - Expression of Interest
- Rochdale Infirmary, Northern Care Alliance NHS Trust - Expression of Interest
- Doncaster and Bassetlaw- Expression of Interest

The anticipated total number of recruitment site will be 10-12. The anticipated number of patients expected from each hospital is 4. This will require 2-3 months. This target was thought to be feasible by the sites approached. The revised end date for recruitment will be end of September 2025.

3. CONCLUSIONS

Due to the request by the MHRA to include a 2-month telephone follow-up the patient evaluation period has now increased to 8 months from 6 months and the protocol amendment requested by CTIS. The recruitment of patient has been delayed by 3 months. We have requested a 6-month extension to allow time for recruiting and assessment patients for 8 months as stipulated by regulatory authorities. As the study has been delayed, this provides a summary of current status, and we propose to submit an update by the end of September containing the recruitment report, highlighting the recruiting problems potential or that may have occurred, the mitigation measures to overcome those problems and a full description of the recruitment by study site.

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