Decision on Optimal Combinatorial Therapies in IMIDS using Systems Approaches

DocTIS

Deliverable 8.4

GRANT AGREEMENT NUMBER	848028
Document	WP8 Mid-Term Recruitment Report
Version	V1.0
Submission Date	04 March 2026
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This Project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 848028

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VERSION	DESCRIPTION OF CHANGE
V1.0	

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1. INTRODUCTION

The aim of Work Package 8 (WP8) of the DocTIS project is to validate the efficacy and safety of a novel combinatorial therapy for immune-mediated inflammatory diseases, building on results from WP4-7. The clinical trial—a Simon two-stage adaptive basket design assessing the addition of tocilizumab (IL-6 receptor inhibitor) to a TNF inhibitor in RA and PsA, with remission at 24 weeks as the primary endpoint—was approved by the DocTIS GA in April 2024. The Independent Data Monitoring Committee has reviewed and approved the design, protocol, and planned analyses.

Regulatory submission to the Medicine and Healthcare Products Regulatory Authority (MHRA) in the UK was completed in 2024 and was conditionally approved in Dec 2024 with a required amendment to introduce a 60-day post-treatment telephone follow-up.

2. PROGRESS FROM 2025

2.1 REGULATORY APPROVAL

Full approval by the MHRA was granted in March 2025. The first Trial Management Group meeting convened in February 2025. Five UK centres were identified and the trial opened in May 2025, with the first patient screened and recruited in June 2025. The trial team approached a number of additional potential sites in the UK (see Mitigation Strategies below).

The application for regulatory approval in Spain was submitted via Clinical Trial Information System (CTIS) in 1st April 2025, after the MHRA approval. After minor protocol queries from the EU regulator, CTIS indicated evaluation in the week of 19 May 2025 with approval expected by June 2025. However, the submission was not accepted as a low-intervention study in the EU, nd required a resubmission process. Final approval was granted in October 2025. Vall d'Hebron Research Institute coordinated two committed recruitment sites in Spain.

2.2 6-MONTH NO-COST EXTENSION

Due to the delays described above, a 6 month no-cost extension was requested in June 2025 and formally approved in December 2025. The following timelines were updated as a result of this extension:

- End of DocTIS grant: 30 June 2026
- Anticipated end date of recruitment: 31 December 2025
- Treatment phase completed: end of June 2026
- Last assessment: end of June 2026
- Database locked and analysis of primary endpoint result: Jul/Aug 2026
- Publication prepared for submission: Sep 2026

2.3 GENERAL ASSEMBLY 27 JAN 2026

At the DocTIS General Assembly in Jan 26, Prof. Choy proposed extending recruitment until 13 February 2026 to maximize enrolment, noting that treatment and follow-up would continue until mid-August 2026, with final analysis immediately thereafter.

The aim was to recruit 20 Rheumatoid Arthritis patients and 7-9 Psoriatic Arthritis patients. This would generate sufficient data to report the primary scientific objective and the strongest preclinical signal, while limiting PsA recruitment to reaching the first-stage efficacy signal. This would result in approximately 29 patients instead of the originally planned 40 in the protocol.

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2.4 SITES AND PATIENT RECRUITMENT

The first contract between the Sponsor and a participating centre was finalized and signed with Cardiff and Vale University Health Board in April 2025, immediately upon Regulatory approval. Site initiation training was conducted on 24 Apr 2025 and trial recruitment was opened in May 2025. The first patient was recruited in June 2025 from Cardiff and Vale University Health Board.

A list of UK site training dates is shown below:

- Cardiff & Vale University Health Board: 24 April 2025
- Aneurin Bevan University Health Board: 28 April 2025
- Brighton and Sussex University Hospitals NHS Trust: 23 July 2025
- Swansea Bay University Health Board: 29 July 2025
- Cwm Taf Morgannwg University Health Board: 15 October 2025
- Lewisham and Greenwich NHS Trust: 16 October 2025

2 participating centres in Spain were added to the trial, following CTIS approval (see above). Site training for these sites was conducted on:

- Vall d'Hebron University Hospital: 27 November 2025
- Germans Trias I Pujol Hospital: 20 Jan 2026

MITIGATION

Work package 8 was delayed due to regulators in the UK and EU (through CTIS) requesting protocol amendments to be made before final approval. To mitigate against the impact of the delay, more sites in the UK needed to be recruited and more patients were recruited in Spain in the two sites.

To accelerate the contractual processes and initial treatment, the trial team incentivised sites in UK and Spain to include staff time to actively screen for patients. Due to full support of the lead investigator site (VHIR), we were able to include some patients in this site where no costs for trial drugs were incurred.

In July 2025, to further mitigate the effect of regulatory delays, 5 additional sites were approached to consider participating in the clinical trial in the UK. These were:

- University Hospital of Lewisham – agreed to participate
- University of Sheffield
- Portsmouth University Hospital NHS Trust
- Rochdale Infirmary, Northern Care Alliance NHS Trust
- Doncaster and Bassetlaw NHS Trust

A recruitment target of 3-4 patients per site was considered to be feasible by the sites – support for the trial was dependent on approval of a no-cost extensión to the trial.
In September 2025, 4 out of the 5 additional sites declined to participate in the trial as the end date for the trial had not been extended. Approval for the 6-month extension of the clinical trial was granted in December 2025.
In order to encourage recruitment, and in addition to the monthly Trial Management meetings, an investigator meeting was held at the American College for Rheumatology Annual Scientific Congress in Chicago in November 2025. Investigators from 4 sites attended in person and the summary of the meeting was discussed at the Trial Management meeting in December 2025 for sites that could not attend in person. In total, 8 medical centres (6 UK and 2 Spain) participated in the DocTIS clinical trial.

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The following table shows the number of patients recruited in UK and Spain, and the treatment status of the patients as of 13 Feb 2026.

	Rheumatoid Arthritis (RA)	Psoriatic Arthritis (PSA)
UK		
Signed informed consent and recruited to the trial	10	4
Currently on Treatment	9	4
Discontinued Treatment	0	0
SPAIN		
Signed informed consent and recruited to the trial	5	3
Currently on Treatment	4	3
Discontinued Treatment	0	0
TOTAL (patients consented)	15	7

The following table shows the breakdown of recruitment by disease at each site:

Patient recruited by sites	PsA	RA	Grand Total
Aneurin Bevan	1		1
Germans Trias I Pujol	1	2	3
Lewisham		2	2
Royal Glamorgan	2	4	6
Swansea Bay		4	4
UHW	1		1
Val d 'Hebron	2	3	5
Grand Total	**7**	**15**	**22**

3. CONCLUSIONS

Despite significant regulatory delay, the number of recruited patients: 15 RA and 7 PsA patients, is sufficient for interim analysis. If no patient achieves remission, then futility will be declared. 18 completed and evaluated RA patients would be required to achieve the planned statistical power, as the protocol allowed for 10% drop out, i.e., 2 patients. However, at 15 RA patients, the expected number of patients that will achieve remission is 30% i.e. 5 patients. If at least 5 RA patients achieve remission, then there is sufficient evidence to support that combining IL-6 and TNF inhibitors is efficacious and would warrant a definitive randomised control trial to confirm the observation.

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