Clinical trial results:
Clinical effectiveness of standard step up care (methotrexate) compared to early combination DMARD therapy with standard step up care compared to early use of TNF inhibitors with standard step up care for the treatment of moderate to Severe Psoriatic arthritis: a 3-arm parallel group randomised controlled trial.

Summary

EudraCT number	2017-004542-24
Trial protocol	GB
Global end of trial date	31 October 2024

Results information

Result version number	v1 (current)
This version publication date	17 June 2026
First version publication date	17 June 2026

Trial information

Trial identification

Sponsor protocol code	N/A

Additional study identifiers

ISRCTN number	ISRCTN70603700
ClinicalTrials.gov id (NCT number)	NCT03739853
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Oxford
Sponsor organisation address	Research Governance, Ethics and Assurance Team, Boundary Brook House, Churchill Drive, Headington, Oxford, United Kingdom, OX3 7LQ
Public contact	Clinical Trials and Research Govern, University of Oxford, 44 1865616480, ctrg@admin.ox.ac.uk
Scientific contact	Clinical Trials and Research Govern, University of Oxford, 44 1865616480, ctrg@admin.ox.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 December 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 October 2024
Global end of trial reached?	Yes
Global end of trial date	31 October 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the initial effectiveness of early combination DMARD therapy (arm 2) and early use of TNF inhibitors (arm 3) with standard step up care (received in the TWiCs cohort; arm 1).

Protection of trial subjects:

All patients received active treatment and it was open label so that they could interpret any side effects or issues.
No sensitive questionnaires included.

Background therapy:

Not applicable

Evidence for comparator:

The optimal treatment strategy, and how to personalise this in a heterogeneous condition such as psoriatic arthritis remains unknown as highlighted in recent international treatment recommendations. Current guidance suggests more intensive therapy for those with poor prognostic factors, but this is not evidence-based. Since the systematic literature reviews informing these treatment recommendations have been published, one Dutch study comparing combination DMARDs (methotrexate plus leflunomide) to methotrexate alone, showed improved clinical response on the combination but with a higher risk of side effects. Two recent studies have compared early biologics (golimumab in GolMePsA and secukinumab in STAMP) with methotrexate and steroids in early PsA. These studies did not show any significant difference after 24 weeks of treatment when including all newly diagnosed PsA patients with at least 2 active peripheral joints. All medications used in the study were routinely used in PsA treatment in the UK and internationally.

Actual start date of recruitment	31 July 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 192
Worldwide total number of subjects	192
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	192
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment at 9 UK sites from 2018-2023.

Pre-assignment

Screening details:

Eligible patients were recruited from participants in the MONITOR-PsA cohort. 310 patients across 9 sites were screened for eligibility. 118 patients were excluded (41 not poor prognosis, 11 no consent for RCTs, 10 axial disease, 20 safety issues, 9 COVID pause, 1 pregnancy, 11 declined, 15 other)

Period 1

Period 1 title	Baseline (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Standard care

Arm description:

Patient randomised to arm 1 received standard 'step-up' therapy in line with the cohort. While physician discretion is used, the most common initial therapy is methotrexate alone, involving monotherapy methotrexate (15mg/week rising to 25mg/week as tolerated by week 8 of therapy either oral or subcutaneous) unless contraindicated. In cases of inefficacy or intolerance to the provided medication, treatment could be escalated following a step-up approach and the National Institute for Health and Clinical Excellence (NICE) recommendations14 for the use of biologics. This was classified as rescue therapy.

Arm type	Active comparator
Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Solution for injection
Routes of administration	Oral use, Subcutaneous use

Dosage and administration details:

the most common initial therapy is methotrexate alone, involving monotherapy methotrexate (15mg/week rising to 25mg/week as tolerated by week 8 of therapy either oral or subcutaneous) unless contraindicated.

Arm title	Combo DMARD

Arm description:

Arm 2 was the combination DMARD arm. All participants were prescribed methotrexate with an additional csDMARD (either sulfasalazine increasing to 2g, potentially up to 3g daily or leflunomide 10-20mg daily) at baseline, staggering the start of these therapies by one week. In cases of inefficacy or intolerance to the provided medication, treatment could be escalated following a step-up approach and the National Institute for Health and Clinical Excellence (NICE) recommendations14 for the use of biologics. This was classified as rescue therapy.

Arm type	Experimental
Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection, Tablet
Routes of administration	Oral use, Subcutaneous use

Dosage and administration details:

the most common initial therapy is methotrexate alone, involving monotherapy methotrexate (15mg/week rising to 25mg/week as tolerated by week 8 of therapy either oral or subcutaneous) unless

contraindicated.

Investigational medicinal product name	Sulfasalazine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

sulfasalazine increasing to 2g, potentially up to 3g daily

Investigational medicinal product name	Leflunomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

leflunomide 10-20mg daily

Arm title	early TNFi

Arm description:

Arm 3 was the early biologic arm. All participants were prescribed weekly methotrexate with a TNF inhibitor (adalimumab 40mg given every two weeks) at baseline staggering the start of these therapies by one week. Treatment with adalimumab at standard dosing was continued until week 24 then tapered by extending the dose interval to week 28 and week 32. Adalimumab was stopped completely after week 32 and participants continued methotrexate as standard care. In cases of inefficacy or intolerance to the provided medication, treatment could be escalated following a step-up approach and the National Institute for Health and Clinical Excellence (NICE) recommendations14 for the use of biologics. This was classified as rescue therapy.

Arm type	Experimental
Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection, Tablet
Routes of administration	Oral use, Subcutaneous use

Dosage and administration details:

the most common initial therapy is methotrexate alone, involving monotherapy methotrexate (15mg/week rising to 25mg/week as tolerated by week 8 of therapy either oral or subcutaneous) unless contraindicated.

Investigational medicinal product name	Adalimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Adalimumab 40mg given every two weeks at baseline staggering the start of these therapies by one week. Treatment with adalimumab at standard dosing was continued until week 24 then tapered by extending the dose interval to week 28 and 32. Adalimumab was stopped completely after week 32

Number of subjects in period 1	Standard care	Combo DMARD	early TNFi
Started	64	63	65
Completed	57	55	58
Not completed	7	8	7
Consent withdrawn by subject	6	3	3

Declined treatment offered	1	5	4

Baseline characteristics

Reporting groups	
Reporting group title	Standard care

Reporting group description:

Patient randomised to arm 1 received standard 'step-up' therapy in line with the cohort. While physician discretion is used, the most common initial therapy is methotrexate alone, involving monotherapy methotrexate (15mg/week rising to 25mg/week as tolerated by week 8 of therapy either oral or subcutaneous) unless contraindicated. In cases of inefficacy or intolerance to the provided medication, treatment could be escalated following a step-up approach and the National Institute for Health and Clinical Excellence (NICE) recommendations14 for the use of biologics. This was classified as rescue therapy.

Reporting group title	Combo DMARD

Reporting group description:

Arm 2 was the combination DMARD arm. All participants were prescribed methotrexate with an additional csDMARD (either sulfasalazine increasing to 2g, potentially up to 3g daily or leflunomide 10-20mg daily) at baseline, staggering the start of these therapies by one week. In cases of inefficacy or intolerance to the provided medication, treatment could be escalated following a step-up approach and the National Institute for Health and Clinical Excellence (NICE) recommendations14 for the use of biologics. This was classified as rescue therapy.

Reporting group title	early TNFi

Reporting group description:

Arm 3 was the early biologic arm. All participants were prescribed weekly methotrexate with a TNF inhibitor (adalimumab 40mg given every two weeks) at baseline staggering the start of these therapies by one week. Treatment with adalimumab at standard dosing was continued until week 24 then tapered by extending the dose interval to week 28 and week 32. Adalimumab was stopped completely after week 32 and participants continued methotrexate as standard care. In cases of inefficacy or intolerance to the provided medication, treatment could be escalated following a step-up approach and the National Institute for Health and Clinical Excellence (NICE) recommendations14 for the use of biologics. This was classified as rescue therapy.

Reporting group values	Standard care	Combo DMARD	early TNFi
Number of subjects	64	63	65
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
median	50	51	48
inter-quartile range (Q1-Q3)	34 to 57	37 to 60	34 to 57
Gender categorical			
Gender			
Units: Subjects			
Female	31	33	28
Male	33	30	37
BMI			
BMI categorites			
Units: Subjects			
Underweight/Normal	13	9	15
Overweight	21	28	22
Obese	30	25	26
Not recorded	0	1	2
Enthesitis			
Presence of enthesitis			

Units: Subjects			
Yes	33	30	33
No	31	33	30
Not recorded	0	0	2
Tender joint count			
Tender joint count			
Units: Joints			
median	9	10	10
inter-quartile range (Q1-Q3)	5 to 21.5	5 to 17	6 to 18
Swollen joint count			
Swollen joint count			
Units: Joints			
median	5	5	5
inter-quartile range (Q1-Q3)	2 to 8.5	3 to 9	3 to 9
PASDAS			
PsA disease activity score			
Units: units			
arithmetic mean	5.6	5.5	5.7
standard deviation	± 1.2	± 1.3	± 1.1
PsAID			
PsA impact of disease questionnaire			
Units: units			
arithmetic mean	5.4	5.3	5.5
standard deviation	± 2.1	± 2.2	± 2.0

Reporting group values	Total		
Number of subjects	192		
Age categorical Units: Subjects			

Age continuous Units: years median inter-quartile range (Q1-Q3)	-		
Gender categorical			
Gender			
Units: Subjects			
Female	92		
Male	100		
BMI			
BMI categorites			
Units: Subjects			
Underweight/Normal	37		
Overweight	71		
Obese	81		
Not recorded	3		
Enthesitis			
Presence of enthesitis			
Units: Subjects			
Yes	96		
No	94		

Not recorded	2		

Tender joint count			
Tender joint count			
Units: Joints			
median			
inter-quartile range (Q1-Q3)	-		
Swollen joint count			
Swollen joint count			
Units: Joints			
median			
inter-quartile range (Q1-Q3)	-		
PASDAS			
PsA disease activity score			
Units: units			
arithmetic mean			
standard deviation	-		
PsAID			
PsA impact of disease questionnaire			
Units: units			
arithmetic mean			
standard deviation	-		

Subject analysis sets	
Subject analysis set title	ITT analysis
Subject analysis set type	Intention-to-treat
Subject analysis set description: Intention to treat	

Reporting group values	ITT analysis		
Number of subjects	192		
Age categorical Units: Subjects			

Age continuous Units: years			
median	49		
inter-quartile range (Q1-Q3)	34 to 58		
Gender categorical			
Gender			
Units: Subjects			
Female	92		
Male	100		
BMI			
BMI categorites			
Units: Subjects			
Underweight/Normal	37		
Overweight	71		
Obese	81		

Not recorded	3		
Enthesitis			
Presence of enthesitis			
Units: Subjects			
Yes	96		
No	94		
Not recorded	2		
Tender joint count			
Tender joint count			
Units: Joints			
median	10		
inter-quartile range (Q1-Q3)	5 to 18		
Swollen joint count			
Swollen joint count			
Units: Joints			
median	5		
inter-quartile range (Q1-Q3)	3 to 9		
PASDAS			
PsA disease activity score			
Units: units			
arithmetic mean	5.6		
standard deviation	± 1.2		
PsAID			
PsA impact of disease questionnaire			
Units: units			
arithmetic mean	5.4		
standard deviation	± 2.1		

End points

End points reporting groups

Reporting group title	Standard care

Reporting group description:

Patient randomised to arm 1 received standard 'step-up' therapy in line with the cohort. While physician discretion is used, the most common initial therapy is methotrexate alone, involving monotherapy methotrexate (15mg/week rising to 25mg/week as tolerated by week 8 of therapy either oral or subcutaneous) unless contraindicated. In cases of inefficacy or intolerance to the provided medication, treatment could be escalated following a step-up approach and the National Institute for Health and Clinical Excellence (NICE) recommendations14 for the use of biologics. This was classified as rescue therapy.

Reporting group title	Combo DMARD

Reporting group description:

Arm 2 was the combination DMARD arm. All participants were prescribed methotrexate with an additional csDMARD (either sulfasalazine increasing to 2g, potentially up to 3g daily or leflunomide 10-20mg daily) at baseline, staggering the start of these therapies by one week. In cases of inefficacy or intolerance to the provided medication, treatment could be escalated following a step-up approach and the National Institute for Health and Clinical Excellence (NICE) recommendations14 for the use of biologics. This was classified as rescue therapy.

Reporting group title	early TNFi

Reporting group description:

Arm 3 was the early biologic arm. All participants were prescribed weekly methotrexate with a TNF inhibitor (adalimumab 40mg given every two weeks) at baseline staggering the start of these therapies by one week. Treatment with adalimumab at standard dosing was continued until week 24 then tapered by extending the dose interval to week 28 and week 32. Adalimumab was stopped completely after week 32 and participants continued methotrexate as standard care. In cases of inefficacy or intolerance to the provided medication, treatment could be escalated following a step-up approach and the National Institute for Health and Clinical Excellence (NICE) recommendations14 for the use of biologics. This was classified as rescue therapy.

Subject analysis set title	ITT analysis
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Intention to treat

Primary: PASDAS at week 24

End point title	PASDAS at week 24

End point description:

PASDAS at 24 weeks

End point type	Primary

End point timeframe:

24 weeks

End point values	Standard care	Combo DMARD	early TNFi	ITT analysis
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	39	47	53	139
Units: units				
arithmetic mean (standard deviation)	4.7 (± 1.5)	4.0 (± 1.5)	3.6 (± 1.9)	4.03 (± 1.7)

Statistical analyses

Statistical analysis title	PASDAS at week 24
Statistical analysis description:	
Primary outcome - ANOVA across all 3 groups	
Comparison groups	Standard care v Combo DMARD v early TNFi
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012
Method	ANOVA

Statistical analysis title	Combo DMARD vs standard care
Comparison groups	Standard care v Combo DMARD
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0096
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	-0.19

Statistical analysis title	TNF vs Standard Care
Comparison groups	early TNFi v Standard care
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0006
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.78
upper limit	-0.49

Statistical analysis title	TNF vs Combo DMARD
Comparison groups	Combo DMARD v early TNFi

Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1952
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	0.22

Secondary: PASDAS at week 48	
End point title	PASDAS at week 48
End point description: PASDAS at week 48	
End point type	Secondary
End point timeframe: 48 week	

End point values	Standard care	Combo DMARD	early TNFi	ITT analysis
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	45	45	49	139
Units: units				
arithmetic mean (standard deviation)	4.1 (± 1.8)	3.8 (± 1.5)	3.5 (± 1.7)	0 (± 0)

Statistical analyses

Statistical analysis title	Combo DMARD vs standard care
Comparison groups	Combo DMARD v Standard care
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1444
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.11
upper limit	0.16

Statistical analysis title	TNF vs Standard Care
Comparison groups	Standard care v early TNFi
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0298
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.31
upper limit	-0.07

Secondary: MDA at week 24

End point title	MDA at week 24

End point description:

End point type	Secondary

End point timeframe:

24 week

End point values	Standard care	Combo DMARD	early TNFi	ITT analysis
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	42	51	54	147
Units: Individual				
Achieved	4	15	18	37
Not achieved	38	36	36	110

Statistical analyses

No statistical analyses for this end point

Secondary: MDA at week 48

End point title	MDA at week 48

End point description:

MDA at week 48

End point type	Secondary

End point timeframe: week 48

End point values	Standard care	Combo DMARD	early TNFi	ITT analysis
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	44	45	51	140
Units: Individual				
Not achieved	33	33	35	101
Achieved	11	12	16	39

Statistical analyses

No statistical analyses for this end point

Secondary: PSAID at week 24	
End point title	PSAID at week 24
End point description: PSAID at week 24	
End point type	Secondary
End point timeframe: 24 week	

End point values	Standard care	Combo DMARD	early TNFi	ITT analysis
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	43	51	54	148
Units: units				
arithmetic mean (standard deviation)	3.8 (± 2.1)	3.5 (± 2.4)	3.1 (± 2.5)	0 (± 0)

Statistical analyses

Statistical analysis title	Combo DMARD vs Standard Care
Comparison groups	Combo DMARD v Standard care
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5187
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.27

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.07
upper limit	0.54

Statistical analysis title	TNF vs Standard Care
Comparison groups	Standard care v early TNFi
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0795
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.53
upper limit	0.09

Secondary: PSAID at week 48	
End point title	PSAID at week 48
End point description: PSAID at week 48	
End point type	Secondary
End point timeframe: 48 week	

End point values	Standard care	Combo DMARD	early TNFi	ITT analysis
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	45	46	51	142
Units: units				
arithmetic mean (standard deviation)	3.4 (± 2.5)	3.3 (± 2.6)	3.0 (± 2.5)	0 (± 0)

Statistical analyses

Statistical analysis title	Combination DMARD vs Standard Care
Comparison groups	Standard care v Combo DMARD

Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4229
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.15
upper limit	0.48

Statistical analysis title	TNF vs Standard Care
Comparison groups	Standard care v early TNFi
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2058
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.33
upper limit	0.29

Secondary: PASDAS (Good) at week 24

End point title	PASDAS (Good) at week 24
End point description:	

End point type	Secondary
End point timeframe:	
24 week	

End point values	Standard care	Combo DMARD	early TNFi	ITT analysis
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	64	63	65	192
Units: Individual				
Good	3	15	24	42

Statistical analyses

Statistical analysis title	Combination DMARD vs Standard Care
Comparison groups	Standard care v Combo DMARD
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0074
Method	Mixed models analysis
Parameter estimate	Odds ratio (OR)
Point estimate	6.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.63
upper limit	23.67

Statistical analysis title	TNF vs Standard Care
Comparison groups	Standard care v early TNFi
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003
Method	Mixed models analysis
Parameter estimate	Odds ratio (OR)
Point estimate	11.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.98
upper limit	40.97

Statistical analysis title	TNF vs Combo DMARD
Comparison groups	Combo DMARD v early TNFi

Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1579
Method	Mixed models analysis
Parameter estimate	Odds ratio (OR)
Point estimate	1.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	4.21

Secondary: PASDAS (Good) at week 48

End point title	PASDAS (Good) at week 48
End point description:	

End point type	Secondary
End point timeframe:	
48 week	

End point values	Standard care	Combo DMARD	early TNFi	ITT analysis
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	64	63	65	192
Units: Individual				
Good	11	15	20	46

Statistical analyses

Statistical analysis title	Combo DMARD vs Standard Care
Comparison groups	Standard care v Combo DMARD
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2271
Method	Mixed models analysis
Parameter estimate	Odds ratio (OR)
Point estimate	1.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	4.53

Statistical analysis title	TNF vs Standard Care
Comparison groups	Standard care v early TNFi
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.107
Method	Mixed models analysis
Parameter estimate	Odds ratio (OR)
Point estimate	2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	5.18

Secondary: PASDAS (Moderate and Good) at week 24	
End point title	PASDAS (Moderate and Good) at week 24
End point description:	

End point type	Secondary
End point timeframe:	
24 week	

End point values	Standard care	Combo DMARD	early TNFi	ITT analysis
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	64	63	65	192
Units: Individual				
Moderate and Good	20	29	39	88

Statistical analyses

Statistical analysis title	Combination DMARD vs Standard Care
Comparison groups	Standard care v Combo DMARD
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2137
Method	Mixed models analysis
Parameter estimate	Odds ratio (OR)
Point estimate	1.81

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	4.59

Statistical analysis title	TNF vs Standard Care
Comparison groups	Standard care v early TNFi
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0217
Method	Mixed models analysis
Parameter estimate	Odds ratio (OR)
Point estimate	3.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.18
upper limit	8.45

Secondary: PASDAS (Moderate and Good) at week 48	
End point title	PASDAS (Moderate and Good) at week 48
End point description:	

End point type	Secondary
End point timeframe:	
48 week	

End point values	Standard care	Combo DMARD	early TNFi	ITT analysis
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	64	63	65	192
Units: Individual				
Moderate and Good	25	31	37	93

Statistical analyses

Statistical analysis title	Combo DMARD vs Standard Care
Comparison groups	Standard care v Combo DMARD

Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1281
Method	Mixed models analysis
Parameter estimate	Odds ratio (OR)
Point estimate	2.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	5.38

Statistical analysis title	TNF vs Standard Care
Comparison groups	Standard care v early TNFi
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.105
Method	Mixed models analysis
Parameter estimate	Odds ratio (OR)
Point estimate	2.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	5.8

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline to week 48

Adverse event reporting additional description:

Adverse events of special interest and SAEs

Assessment type	Systematic

Dictionary used

Dictionary name	DMARD side effects
Dictionary version	1

Reporting groups

Reporting group title	Standard care

Reporting group description:

Patient randomised to arm 1 received standard 'step-up' therapy in line with the cohort. While physician discretion is used, the most common initial therapy is methotrexate alone, involving monotherapy methotrexate (15mg/week rising to 25mg/week as tolerated by week 8 of therapy either oral or subcutaneous) unless contraindicated. In cases of inefficacy or intolerance to the provided medication, treatment could be escalated following a step-up approach and the National Institute for Health and Clinical Excellence (NICE) recommendations14 for the use of biologics. This was classified as rescue therapy.

Reporting group title	Combo DMARD

Reporting group description:

Arm 2 was the combination DMARD arm. All participants were prescribed methotrexate with an additional csDMARD (either sulfasalazine increasing to 2g, potentially up to 3g daily or leflunomide 10-20mg daily) at baseline, staggering the start of these therapies by one week. In cases of inefficacy or intolerance to the provided medication, treatment could be escalated following a step-up approach and the National Institute for Health and Clinical Excellence (NICE) recommendations14 for the use of biologics. This was classified as rescue therapy.

Reporting group title	early TNFi

Reporting group description:

Arm 3 was the early biologic arm. All participants were prescribed weekly methotrexate with a TNF inhibitor (adalimumab 40mg given every two weeks) at baseline staggering the start of these therapies by one week. Treatment with adalimumab at standard dosing was continued until week 24 then tapered by extending the dose interval to week 28 and week 32. Adalimumab was stopped completely after week 32 and participants continued methotrexate as standard care. In cases of inefficacy or intolerance to the provided medication, treatment could be escalated following a step-up approach and the National Institute for Health and Clinical Excellence (NICE) recommendations14 for the use of biologics. This was classified as rescue therapy.

Serious adverse events	Standard care	Combo DMARD	early TNFi
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 64 (3.13%)	0 / 63 (0.00%)	2 / 65 (3.08%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Cerebellar haemorrhage			

subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastroenteritis			
subjects affected / exposed	0 / 64 (0.00%)	0 / 63 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Perineal abscess			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 64 (0.00%)	0 / 63 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Standard care	Combo DMARD	early TNFi
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 64 (29.69%)	20 / 63 (31.75%)	18 / 65 (27.69%)
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 64 (14.06%)	11 / 63 (17.46%)	5 / 65 (7.69%)
occurrences (all)	9	11	5
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	19 / 64 (29.69%)	20 / 63 (31.75%)	15 / 65 (23.08%)
occurrences (all)	19	20	15
Diarrhoea			
subjects affected / exposed	6 / 64 (9.38%)	8 / 63 (12.70%)	6 / 65 (9.23%)
occurrences (all)	6	8	6
Hepatobiliary disorders			

Liver function test abnormal subjects affected / exposed occurrences (all)	11 / 64 (17.19%) 11	19 / 63 (30.16%) 19	18 / 65 (27.69%) 18
Infections and infestations Infection subjects affected / exposed occurrences (all)	3 / 64 (4.69%) 3	3 / 63 (4.76%) 3	6 / 65 (9.23%) 6

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 August 2018	Change in sample testing to BRS guidelines. Change to sponsor address, LC's phone number, NHS digital added. The title has been changed to include 'moderate' . The PIS has also been submitted in this amendment to remove 'at least 24 hours'
03 May 2019	PIS - GDPR added to Arm 2 and Arm 3 of the Patient Information Sheet. Protocol changes to include the two new sites, Removal of BASMI at 12,24,36 and 72 weeks, only to be performed at baseline, 48 weeks and thereafter.
03 July 2019	Manufacturing documents required by the MHRA.
08 March 2022	Protocol has been updated to include: addition of information about creation and storage of datasets, clarification of SAE reporting requirements, acceptable methods of contraception added, discontinuation of trial treatment in pregnancy and information added relating to the reporting procedure for pregnancy, reporting obligations to AbbVie, correction to Schedule to match body of protocol and due to SPEED being a pragmatic study, where deviations from this standard national policy on blood monitoring are implemented by the NHS hospitals, this may change in accordance with local guidelines (allowance of blood monitoring to be within 3 months not just 1 month) monitoring will remain in line with local hospital policy. Update to SmPC for Adalimumab and Methotrexate which include changes to the RSI (for which we seek approval) but that do not affect risk/benefit assessment. PIS arm 2 and 3 now have information related to pregnancies. In arm 3 additional information has been added for patients partners who become pregnant, the associated reporting requirement and contraception examples provided. A new combined PIS and ICF has been generated for patients pregnant partners. Addition of importer for compliance with new regulations to import investigational medicinal for clinical research into GB from the EU.
10 March 2023	Protocol changes: Planned sample size has changed to 192, follow up duration has changed. Planned end date has changed to October 2023. Treatment duration changed to min36-max48 weeks. Primary and secondary outcomes have been clarified with new evidence in mind. Clarification provided that some patients who are recruited late into the trial will only reach the week 36 assessment visit. Statistics section updated to only include information on the primary outcome and updated to include the change to the way the new primary outcome is specified. Following information from new publication the primary outcome has changed to continuous outcome. PIS arm 2 and 3 have been updated to reflect protocol changes.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
20 March 2020	Covid-19 study pause	29 July 2020

Notes:

Limitations and caveats

None reported