Clinical trial results:
Tight control dose reductions of biologics in psoriasis patients with low disease activity: a randomized pragmatic trial.

Summary

EudraCT number	2015-000943-17
Trial protocol	NL
Global end of trial date	01 August 2019

Results information

Result version number	v1 (current)
This version publication date	09 January 2021
First version publication date	09 January 2021

Trial information

Trial identification

Sponsor protocol code	NL54557.091.15

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02602925
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Radboud University Nijmegen Medical Centre
Sponsor organisation address	René Descartesdreef 1, Nijmegen, Netherlands, 6526GL
Public contact	Elke de Jong, Radboud University Nijmegen Medical Centre, +31 243613342, Elke.deJong@radboudumc.nl
Scientific contact	Elke de Jong, Radboud University Nijmegen Medical Centre, +31 243613342, Elke.deJong@radboudumc.nl

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	22 July 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 July 2018
Global end of trial reached?	Yes
Global end of trial date	01 August 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

We aim to investigate whether we could taper the biologics dose in psoriasis patietns with stable disease-activity and good quality of life. The primary research question for this proposal is: Is a biologics dose tapering strategy non-inferior to usual care with respect to disease activity?

Protection of trial subjects:

All patients who are eligible for this study will be asked by their dermatologist and they will receive oral and written information from the local investigator. The investigator will obtain written informed consent and the patient will be randomized. The schedule of their biological will be explained depending on which biologic the patient uses.

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons. When subjects are withdrawn from the study, they will not be replaced.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 January 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 120
Worldwide total number of subjects	120
EEA total number of subjects	120

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)	86
From 65 to 84 years	34
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

All patients who are eligible for this study will be asked by their dermatologist and they will receive oral and written information from the local investigator. The investigator will obtain written informed consent and the patient will be randomized.

Pre-assignment

Screening details:

Patients 18 years or older with plaque psoriasis and stable low disease activity using standard doses of adalimumab, etanercept, or ustekinumab for at least 6 months were included. Low disease activity is described as a PASI score of 5 or lower at 2 subsequent visits in the past 6 months and a DLQI score of 5 or lower at study inclusion.

Pre-assignment period milestones

Number of subjects started	120
Number of subjects completed	120

Period 1

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

Blinding implementation details:

Not blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Randomized to usual care

Arm description:

Patients continued to receive usual care

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Randomized to dose reduction

Arm description:

The doses of etanercept, adalimumab or ustekinumab are lowered according to a predefined schedule

Arm type	Active comparator
Investigational medicinal product name	adalimumab
Investigational medicinal product code	
Other name	Humira
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

The dose will be decreased to 66–70% of the normal dose of the biologic (by interval prolongation with a factor 1.5). After 3 months, if the patients remain in a state of low disease activity, the dose will be further reduced to 50% of the original dose (by doubling the original interval). The interval will be prolonged from 14 to 21 to 28 days.

Investigational medicinal product name	etanercept
Investigational medicinal product code	
Other name	Enbrel
Pharmaceutical forms	Injection

Routes of administration	Subcutaneous use

Dosage and administration details:

The dose will be decreased to 66–70% of the normal dose of the biologic (by interval prolongation with a factor 1.5). After 3 months, if the patients remain in a state of low disease activity, the dose will be further reduced to 50% of the original dose (by doubling the original interval). The interval will be prolonged stepwise from 7 days to 10 days to 14 days.

Investigational medicinal product name	ustekinumab
Investigational medicinal product code	
Other name	Stelara
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

The dose will be decreased to 66–70% of the normal dose of the biologic (by interval prolongation with a factor 1.5). After 3 months, if the patients remain in a state of low disease activity, the dose will be further reduced to 50% of the original dose (by doubling the original interval). The interval will be stepwise increased from 12 to 18 to 24 weeks

Number of subjects in period 1	Randomized to usual care	Randomized to dose reduction
Started	60	60
Completed	58	53
Not completed	2	7
Protocol violation	1	1
Lost to follow-up	1	1
Protocol deviation	-	5

Baseline characteristics

Reporting groups	
Reporting group title	Randomized to usual care
Reporting group description:	
Patients continued to receive usual care	
Reporting group title	Randomized to dose reduction
Reporting group description:	
The doses of etanercept, adalimumab or ustekinumab are lowered according to a predefined schedule	

Reporting group values	Randomized to usual care	Randomized to dose reduction	Total
Number of subjects	60	60	120
Age categorical Units: Subjects			
Adults (18-64 years)	50	50	100
From 65-84 years	10	10	20
Age continuous			
54.0 [13.2]			
Units: years arithmetic mean standard deviation	57 ± 13.3	53 ± 12.9	--
Gender categorical			
82 (68%) males			
Units: Subjects			
Female	18	20	38
Male	42	40	82

End points

End points reporting groups

Reporting group title	Randomized to usual care
Reporting group description: Patients continued to receive usual care	
Reporting group title	Randomized to dose reduction
Reporting group description: The doses of etanercept, adalimumab or ustekinumab are lowered according to a predefined schedule	

Primary: PASI score (disease activity) at month 12

End point title	PASI score (disease activity) at month 12
End point description:	
End point type	Primary
End point timeframe: PASI score at month 12	

End point values	Randomized to usual care	Randomized to dose reduction		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	53		
Units: PASI number				
median (inter-quartile range (Q1-Q3))	2.1 (0.6 to 3.6)	3.4 (2.2 to 4.5)		

Statistical analyses

Statistical analysis title	Noninferiority analysis
Comparison groups	Randomized to usual care v Randomized to dose reduction
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.05
Method	ANCOVA

Secondary: DLQI (Dermatology Life Quality Index) at month 12

End point title	DLQI (Dermatology Life Quality Index) at month 12
End point description:	
End point type	Secondary

End point timeframe:

DLQI (Dermatology Life Quality Index) at month 12

End point values	Randomized to usual care	Randomized to dose reduction		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	53		
Units: DLQI number				
median (inter-quartile range (Q1-Q3))	0.0 (0.0 to 2.0)	1.0 (0.0 to 2.0)		

Statistical analyses

Statistical analysis title	Noninferiority analysis
Comparison groups	Randomized to usual care v Randomized to dose reduction
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.05
Method	ANCOVA

Secondary: Disease-activity scores (PASI) at each time point (month 3/6/9/12)

End point title	Disease-activity scores (PASI) at each time point (month 3/6/9/12)

End point description:

Reported result is significant difference at month 9

End point type	Secondary

End point timeframe:

Month 3/6/9/12

End point values	Randomized to usual care	Randomized to dose reduction		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	53		
Units: PASI score				
arithmetic mean (confidence interval 95%)	2.3 (1.8 to 2.9)	3.4 (2.8 to 3.9)		

Statistical analyses

Statistical analysis title	Noninferiority analysis
Comparison groups	Randomized to usual care v Randomized to dose reduction
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.05
Method	ANCOVA

Secondary: Proportion of patients with successful dose tapering

End point title	Proportion of patients with successful dose tapering[1]

End point description:

End point type	Secondary

End point timeframe:

After 12 months

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: End point reports on number of patients that succesfully tapered their dose. This is not applicable to patients that continued to receive usual care.

End point values	Randomized to dose reduction			
Subject group type	Reporting group			
Number of subjects analysed	53			
Units: Patients	28			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients with short and persistent flares

End point title	Proportion of patients with short and persistent flares

End point description:

End point type	Secondary

End point timeframe:

During study period

End point values	Randomized to usual care	Randomized to dose reduction		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	53		
Units: Patients				
Short	8	19		
Persistent	5	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Topical corticosteroid use

End point title	Topical corticosteroid use

End point description:

End point type	Secondary

End point timeframe:

During study period (12 months)

End point values	Randomized to usual care	Randomized to dose reduction		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	53		
Units: Patients	21	44		

Statistical analyses

No statistical analyses for this end point

Secondary: Additional methotrexate or acitretin use

End point title	Additional methotrexate or acitretin use

End point description:

End point type	Secondary

End point timeframe:

During study period (12 months)

End point values	Randomized to usual care	Randomized to dose reduction		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	53		
Units: Percentage	12	13		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of severe adverse events (SAEs)

End point title	Number of severe adverse events (SAEs)

End point description:

End point type	Secondary

End point timeframe:

During study period (12 months)

End point values	Randomized to usual care	Randomized to dose reduction		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	53		
Units: Events	6	6		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Over the total study period (12 months)	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	Randomized to usual care
Reporting group description:	
Patients continued to receive usual care	
Reporting group title	Randomized to dose reduction
Reporting group description:	
The doses of etanercept, adalimumab or ustekinumab are lowered according to a predefined schedule	

Serious adverse events	Randomized to usual care	Randomized to dose reduction	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 59 (10.17%)	6 / 59 (10.17%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
grawitz tumor	Additional description: grawitz tumor right kidney		
subjects affected / exposed	0 / 59 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fracture	Additional description: Collum fracture		
subjects affected / exposed	1 / 59 (1.69%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Fasciotomy	Additional description: 4 loge fasciotomie left leg clinically suspected for compartiment syndrome		
subjects affected / exposed	0 / 59 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Percutane intentional extraluminal recanalisation a femorali			
subjects affected / exposed	0 / 59 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident	Additional description: ischaemic CVA brainstem ischaemic CVA left hemisphere		
subjects affected / exposed	1 / 59 (1.69%)	2 / 59 (3.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 59 (1.69%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Meniscus operation	Additional description: partial medial menisectomy		
subjects affected / exposed	0 / 59 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Total knee prothesis			
subjects affected / exposed	1 / 59 (1.69%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotis desobstruction			
subjects affected / exposed	1 / 59 (1.69%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dilatation vascular	Additional description: ballondilatation distale anastomosis fem-fem crossover		
subjects affected / exposed	1 / 59 (1.69%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting	Additional description: motility disorder (pre-existent)		

subjects affected / exposed	1 / 59 (1.69%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis	Additional description: cholangitis		
subjects affected / exposed	0 / 59 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Open wound			
subjects affected / exposed	0 / 59 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Delirium	Additional description: after hospitalisation		
subjects affected / exposed	0 / 59 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cystitis bacterial			
subjects affected / exposed	0 / 59 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 59 (1.69%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Randomized to usual care	Randomized to dose reduction	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 59 (77.97%)	51 / 59 (86.44%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Malignant tumor			
subjects affected / exposed	0 / 59 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	
Nonmelanoma skin cancer			
subjects affected / exposed	1 / 59 (1.69%)	1 / 59 (1.69%)	
occurrences (all)	1	1	
Cardiac disorders			
Cardiovascular disorder			
subjects affected / exposed	3 / 59 (5.08%)	3 / 59 (5.08%)	
occurrences (all)	3	3	
Surgical and medical procedures			
Elective surgery			
subjects affected / exposed[1]	4 / 58 (6.90%)	6 / 53 (11.32%)	
occurrences (all)	4	6	
Blood and lymphatic system disorders			
Infection			
subjects affected / exposed	37 / 59 (62.71%)	40 / 59 (67.80%)	
occurrences (all)	73	70	
Skin and subcutaneous tissue disorders			
Psoriatic arthritis			
subjects affected / exposed	1 / 59 (1.69%)	1 / 59 (1.69%)	
occurrences (all)	1	1	
Skin event			
subjects affected / exposed	7 / 59 (11.86%)	4 / 59 (6.78%)	
occurrences (all)	10	4	
Musculoskeletal and connective tissue disorders			
Musculoskeletal disorder			
subjects affected / exposed	4 / 59 (6.78%)	13 / 59 (22.03%)	
occurrences (all)	4	13	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: not all elective surgery cases were considered SAEs

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

1) Open-label design, 2) an absolute PASI score instead of a relative PASI score, 3) dose reduction led to higher topical treatment use and more visits, 4) for per-dsrug conclusions, study was underpowered, 5) no general flare criterion for psorias

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/32049319

http://www.ncbi.nlm.nih.gov/pubmed/33196101