



## 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
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##### 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
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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 patients 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 When subjects are withdrawn from the study, they will not be replaced.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
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<b>Arm title</b>	Randomized to usual care
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Arm description:

Patients continued to receive usual care

Arm type	No intervention
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No investigational medicinal product assigned in this arm

<b>Arm title</b>	Randomized to dose reduction
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Arm description:

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

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

<b>Number of subjects in period 1</b>	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	57	53	
standard deviation	± 13.3	± 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

<b>End point values</b>	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

<b>Statistical analysis title</b>	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	

<b>End point values</b>	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

<b>Statistical analysis title</b>	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

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### Secondary: Proportion of patients with successful dose tapering

End point title	Proportion of patients with successful dose tapering <sup>[1]</sup>
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End point description:

End point type	Secondary
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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 successfully tapered their dose. This is not applicable to patients that continued to receive usual care.

<b>End point values</b>	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

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### Secondary: Proportion of patients with short and persistent flares

End point title	Proportion of patients with short and persistent flares
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End point description:

End point type	Secondary
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End point timeframe:

During study period

<b>End point values</b>	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)

<b>End point values</b>	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)

<b>End point values</b>	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)
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End point description:

End point type	Secondary
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End point timeframe:

During study period (12 months)

<b>End point values</b>	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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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### Reporting groups

Reporting group title	Randomized to usual care
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Reporting group description:

Patients continued to receive usual care

Reporting group title	Randomized to dose reduction
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Reporting group description:

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

<b>Serious adverse events</b>	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)			
gawritz tumor	Additional description: gawritz 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 meniscectomy		
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 prosthesis			
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	
<b>Hepatobiliary disorders</b>			
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	
<b>Skin and subcutaneous tissue disorders</b>			
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	
<b>Psychiatric disorders</b>			
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	
<b>Infections and infestations</b>			
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 %

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

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### 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-drug conclusions, study was underpowered, 5) no general flare criterion for psoriasis
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Notes:

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### Online references

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

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