



## Clinical trial results:

### A Double Blind, Randomized, Placebo Controlled, Multi-Center Trial of Anti-TNF Chimeric Monoclonal Antibody (Infliximab, Remicade®) in Combination with Methotrexate in Patients with Very Early Inflammatory Arthritis

#### Summary

EudraCT number	2006-002787-26
Trial protocol	AT NL DE ES GR GB
Global end of trial date	31 August 2014

#### Results information

Result version number	v1 (current)
This version publication date	01 November 2018
First version publication date	01 November 2018

#### Trial information

##### Trial identification

Sponsor protocol code	DINORA
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##### Additional study identifiers

ISRCTN number	ISRCTN21272423
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Medical University of Vienna
Sponsor organisation address	Spitalgasse 23, Vienna, Austria, 1090
Public contact	Internal Medicine III, Rheumatology, Medical University of Vienna, 043 14040043010, josef.smolen@wienkav.at
Scientific contact	Internal Medicine III, Rheumatology, Medical University of Vienna, +43 14040043010, josef.smolen@wienkav.at

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	23 February 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 August 2014
Global end of trial reached?	Yes
Global end of trial date	31 August 2014
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the study is to demonstrate that patients with very early arthritis have a higher probability of achieving a state of clinical remission at end of infliximab therapy if treated with infliximab plus MTX when compared to MTX monotherapy or supportive treatment only.

Protection of trial subjects:

Personal data pseudonymized.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 May 2007
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	Spain: 1
Country: Number of subjects enrolled	Netherlands: 28
Country: Number of subjects enrolled	Austria: 29
Country: Number of subjects enrolled	Germany: 23
Country: Number of subjects enrolled	Greece: 3
Country: Number of subjects enrolled	Italy: 6
Worldwide total number of subjects	90
EEA total number of subjects	90

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)	70
From 65 to 84 years	20
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Patients were eligible if they had symptom duration of 2 to 16 weeks with synovial swelling in at least 2 joints (66 joint count) of which a minimum of one joint must have been a metacarpophalangeal, proximal interphalangeal or a metatarsophalangeal (MTP) joint. However, two MTP-joints were considered not sufficient for inclusion.

### Pre-assignment

Screening details:

Two screening visits for symptom duration which must have been 2 weeks at least (subjects did not receive study treatment before 12 weeks of symptom duration) and 16 weeks at most. The 16 weeks included an observation period of at least 2 weeks, as reported by the subject.

### Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Blinding implementation details:

A "double-dummy-like" administration of study medication was pursued. Every patient was treated with tablets containing methotrexate or placebo and with infusions containing infliximab or placebo. The study medication code was kept blinded in patients who discontinued prematurely.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	IFX+MTX

Arm description:

Anti-TNF $\alpha$  chimeric monoclonal antibody infliximab (IFX) in combination with methotrexate (MTX)

Arm type	Experimental
Investigational medicinal product name	Anti-TNF $\alpha$ chimeric monoclonal antibody infliximab (IFX)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Infliximab is a chimeric IgG1 monoclonal antibody manufactured from a recombinant cell line cultured by continuous perfusion. Infliximab (IFX) was administered by intravenous infusions at a dose of 3 mg/kg at 0, 2 and 6 weeks, and at 5 mg/kg every 8 weeks thereafter.

Investigational medicinal product name	Methotrexate (MTX)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Methotrexate (MTX) was dosed orally according to a rapid dose escalation scheme: start at 10 mg/week and increased to 25 mg/week in three steps with 2-week intervals except in cases of intolerance.

<b>Arm title</b>	MTX monotherapy
Arm description:	
Methotrexate (MTX) monotherapy	
Arm type	Experimental

Investigational medicinal product name	Methotrexate (MTX)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Methotrexate (MTX) was dosed orally according to a rapid dose escalation scheme: start at 10 mg/week and increased to 25 mg/week in three steps with 2-week intervals except in cases of intolerance.

<b>Arm title</b>	Placebo
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Arm description:

Placebo

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Intravenous use

Dosage and administration details:

A "double-dummy-like" administration of study medication was pursued. Every patient was treated with tablets containing methotrexate (MTX) or placebo and with infusions containing infliximab (IFX) or placebo.

<b>Number of subjects in period 1</b>	IFX+MTX	MTX monotherapy	Placebo
Started	38	36	16
Completed	14	11	7
Not completed	24	25	9
Consent withdrawn by subject	6	9	1
Adverse event, non-fatal	2	1	1
Accidental unblinding	-	-	1
Unknown	3	2	-
Lost to follow-up	1	2	-
Unable to comply with protocol	-	2	-
Lack of efficacy	12	9	6

## Baseline characteristics

### Reporting groups

Reporting group title	IFX+MTX
Reporting group description: Anti-TNF $\alpha$ chimeric monoclonal antibody infliximab (IFX) in combination with methotrexate (MTX)	
Reporting group title	MTX monotherapy
Reporting group description: Methotrexate (MTX) monotherapy	
Reporting group title	Placebo
Reporting group description: Placebo	

Reporting group values	IFX+MTX	MTX monotherapy	Placebo
Number of subjects	38	36	16
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
arithmetic mean	52.1	52.9	54.4
standard deviation	$\pm 14.1$	$\pm 14$	$\pm 11.2$
Gender categorical Units: Subjects			
Female	26	28	9
Male	12	8	7

Reporting group values	Total		
Number of subjects	90		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	0		

From 65-84 years	0		
85 years and over	0		

Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	63		
Male	27		

## End points

### End points reporting groups

Reporting group title	IFX+MTX
Reporting group description: Anti-TNF $\alpha$ chimeric monoclonal antibody infliximab (IFX) in combination with methotrexate (MTX)	
Reporting group title	MTX monotherapy
Reporting group description: Methotrexate (MTX) monotherapy	
Reporting group title	Placebo
Reporting group description: Placebo	

### Primary: Clinical remission

End point title	Clinical remission
End point description:	
End point type	Primary
End point timeframe: At week 54	

End point values	IFX+MTX	MTX monotherapy	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	38 <sup>[1]</sup>	36 <sup>[2]</sup>	16 <sup>[3]</sup>	
Units: Number of patients in clinical remission				
Clinical remission	12	5	0	
No clinical remission	26	31	16	

Notes:

[1] - Intention to treat

[2] - Intention to treat

[3] - Intention to treat

### Statistical analyses

Statistical analysis title	Primary endpoint
Comparison groups	IFX+MTX v MTX monotherapy v Placebo
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Chi-squared

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

During study period

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	Conducted by Janssen
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Dictionary version	NA
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### Reporting groups

Reporting group title	IFX+MTX
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Reporting group description:

Anti-TNFα chimeric monoclonal antibody infliximab (IFX) in combination with methotrexate (MTX)

Reporting group title	MTX monotherapy
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Reporting group description:

Methotrexate (MTX) monotherapy

Reporting group title	Placebo
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Reporting group description:

Placebo

Serious adverse events	IFX+MTX	MTX monotherapy	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 38 (15.79%)	3 / 36 (8.33%)	3 / 16 (18.75%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Haematuria, followed by a diagnosis of bladder cancer			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertensive episode one hour after the last infusion with study drug			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Myocardial infarction more than half a year after last study drug			

subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Social circumstances			
Fainted during blood collection, prior to administration of study drug			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	0 / 16 (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
Endocrine disorders			
Biliary pancreatitis in a time after the study medication			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	0 / 16 (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
Significantly raised transaminase levels			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	0 / 16 (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
Musculoskeletal and connective tissue disorders			
Significant flare of disease activity			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	0 / 16 (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
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MTX pneumonitis (opportunistic) infection			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	0 / 16 (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
Metabolism and nutrition disorders			

Hyperglycemia			
subjects affected / exposed	0 / 38 (0.00%)	0 / 36 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 38 (0.00%)	0 / 36 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0.03 %

<b>Non-serious adverse events</b>	IFX+MTX	MTX monotherapy	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 38 (89.47%)	32 / 36 (88.89%)	13 / 16 (81.25%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Diseases of circulatory system			
subjects affected / exposed	6 / 38 (15.79%)	7 / 36 (19.44%)	3 / 16 (18.75%)
occurrences (all)	8	10	6
Pregnancy, puerperium and perinatal conditions			
Diseases of genitourinary system (pregnancy, childbirth and puerperium)			
subjects affected / exposed	2 / 38 (5.26%)	2 / 36 (5.56%)	0 / 16 (0.00%)
occurrences (all)	2	4	0
General disorders and administration site conditions			
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified			
subjects affected / exposed	11 / 38 (28.95%)	11 / 36 (30.56%)	5 / 16 (31.25%)
occurrences (all)	21	22	6
Social circumstances			
External causes of morbidity			

subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	0 / 36 (0.00%) 0	0 / 16 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Diseases of respiratory system subjects affected / exposed occurrences (all)	23 / 38 (60.53%) 33	16 / 36 (44.44%) 32	4 / 16 (25.00%) 5
Injury, poisoning and procedural complications Injury, poisoning and certain other consequences of external causes subjects affected / exposed occurrences (all)	6 / 38 (15.79%) 10	3 / 36 (8.33%) 3	0 / 16 (0.00%) 0
Nervous system disorders Disease of the nervous system subjects affected / exposed occurrences (all)	6 / 38 (15.79%) 9	9 / 36 (25.00%) 13	2 / 16 (12.50%) 2
Blood and lymphatic system disorders Disease of blood and blood-forming organs and certain disorders involving the immune mechanism subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	0 / 36 (0.00%) 0	0 / 16 (0.00%) 0
Eye disorders Diseases of the eye and adnexa subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	2 / 36 (5.56%) 3	0 / 16 (0.00%) 0
Skin and subcutaneous tissue disorders Diseases of the skin and subcutaneous tissue subjects affected / exposed occurrences (all)	12 / 38 (31.58%) 18	8 / 36 (22.22%) 14	5 / 16 (31.25%) 8
Endocrine disorders Endocrine, nutritional and metabolic diseases subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	5 / 36 (13.89%) 7	2 / 16 (12.50%) 2
Musculoskeletal and connective tissue disorders Diseases of musculoskeletal system and connective tissue subjects affected / exposed occurrences (all)	15 / 38 (39.47%) 26	9 / 36 (25.00%) 16	6 / 16 (37.50%) 8

Infections and infestations Infections subjects affected / exposed occurrences (all)	19 / 38 (50.00%) 30	9 / 36 (25.00%) 22	3 / 16 (18.75%) 4
Metabolism and nutrition disorders Diseases of the digestive system subjects affected / exposed occurrences (all)	15 / 38 (39.47%) 29	17 / 36 (47.22%) 35	5 / 16 (31.25%) 10

## 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

None reported