



## Clinical trial results:

### ENSAYO CLÍNICO ALEATORIZADO Y CONTROLADO PARA EVALUAR LA EFICACIA DE LA AZATIOPRINA VS. MICOFENOLATO SÓDICO PARA EL TRATAMIENTO DE LA FASE DE INDUCCIÓN Y MANTENIMIENTO DE LA REMISIÓN DE LOS BROTES EXTRA RENALES DEL LUPUS ERITEMATOSO SISTÉMICO.

#### Summary

EudraCT number	2008-008934-35
Trial protocol	ES
Global end of trial date	31 December 2015

#### Results information

Result version number	v1 (current)
This version publication date	27 November 2021
First version publication date	27 November 2021

#### Trial information

##### Trial identification

Sponsor protocol code	ORDI-01
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01112215
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	VHIR
Sponsor organisation address	Passeig Vall Hebron 119-129, Barcelona, Spain, 08035
Public contact	Joaquin Lopez-Soriano, VHIR, joaquin.lopez.soriano@vhir.org
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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	31 December 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	31 December 2015
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To compare the efficacy and safety of enteric-coated mycophenolate sodium (EC-MPS) versus azathioprine (AZA) in patients with active systemic lupus erythematosus (SLE) disease.

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice principles. The study protocol was reviewed and approved by every participant centre.

Patients unable to tolerate the target dose or whose weight was below 50kg remained in the study if they tolerated a minimum daily dose of either 720mg of EC-MPS or 50mg of AZA during the first 6 months. Progressive immunosuppressant dose reduction was allowed after week 24 on a 3- to 6-monthly basis per clinical judgement. Changes in antimalarial and prednisone doses were not restricted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 May 2010
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	Spain: 240
Worldwide total number of subjects	240
EEA total number of subjects	240

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)	240
From 65 to 84 years	0

85 years and over	0
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## Subject disposition

### Recruitment

Recruitment details:

Patients were recruited in 12 University hospitals in Spain: Vall d'Hebron; Sant Joan de Reus; Bellvitge; Arnau de Vilanova (Lleida); Corporació Sanitària Parc Taulí (Sabadell); Josep Trueta (Girona); Clinic (Barcelona); Sant Jaume Hospital (Calella); Figueres; Granollers; Mataró; Miguel Servet (Zaragoza).

### Pre-assignment

Screening details:

Eligible patients were aged  $\geq 18$  years, had an SLE according to the revised ACR classification criteria and moderate-to-severe active disease defined as: a SLE Disease Activity Index 2000 (SLEDAI-2K) total score  $\geq 6$  or at least 1 British Isles Lupus Assessment Group (BILAG) A or 2 BILAG B domain scores at screening.

### 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:

The randomised list, stratified by centre and SLEDAI-2K score (6–9 vs  $\geq 10$ ), was created using computer-generated random number sequences in blocks of 10 by the Vall d'Hebrón Hospital investigational pharmacist, who was blind to patient enrolment. Sequentially numbered, concealed envelopes containing group assignment were provided to the investigators

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Azathioprine

Arm description:

AZA (target dose: 2mg/kg, per thiopurine methyltransferase levels (TPMT)) in addition to background oral prednisone and antimalarial agents

Arm type	Experimental
Investigational medicinal product name	Azathioprine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

AZA (target dose: 2mg/kg, per thiopurine methyltransferase levels (TPMT)) in addition to background oral prednisone and antimalarial agents, Progressive immunosuppressant dose reduction was allowed after week 24 on a 3- to 6-monthly basis per clinical judgement. Changes in antimalarial and prednisone doses were not restricted

<b>Arm title</b>	Mycophenolate
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Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Mycophenolate sodium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Enteric Coated mycophenolate sodium (EC-MPS), target dose: 1440mg/day . Changes in antimalarial and prednisone doses were not restricted

<b>Number of subjects in period 1</b>	Azathioprine	Mycophenolate
Started	120	120
Completed	67	87
Not completed	53	33
Adverse event, serious fatal	1	1
Consent withdrawn by subject	2	2
Adverse event, non-fatal	10	6
Lost to follow-up	2	2
Lack of efficacy	38	22

## Baseline characteristics

### Reporting groups

Reporting group title	Azathioprine
Reporting group description: AZA (target dose: 2mg/kg, per thiopurine methyltransferase levels (TPMT)) in addition to background oral prednisone and antimalarial agents	
Reporting group title	Mycophenolate
Reporting group description: -	

Reporting group values	Azathioprine	Mycophenolate	Total
Number of subjects	120	120	240
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	40.9	42.1	
standard deviation	± 12.9	± 13.9	-
Gender categorical Units: Subjects			
Female	111	108	219
Male	9	12	21

## End points

### End points reporting groups

Reporting group title	Azathioprine
Reporting group description: AZA (target dose: 2mg/kg, per thiopurine methyltransferase levels (TPMT)) in addition to background oral prednisone and antimalarial agents	
Reporting group title	Mycophenolate
Reporting group description: -	

### Primary: Clinical remission 3 motnhs

End point title	Clinical remission 3 motnhs
End point description: The primary efficacy endpoints were the proportion of patients achieving at 3 and 24 months, at least 8 consecutive weeks of clinical remission (CR), defined as a clinical SLEDAI-2K=0, where serology was permitted (maximum SLEDAI=4) following the later Zen et al equivalent definition, in the absence of any BILAG A, B or C score.	
End point type	Primary
End point timeframe: 3 motnhs	

End point values	Azathioprine	Mycophenolate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	120		
Units: percent				
number (not applicable)	19.2	32.5		

### Statistical analyses

Statistical analysis title	SLEDAI 3months
Comparison groups	Azathioprine v Mycophenolate
Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.034
Method	t-test, 2-sided

### Primary: Clinical remission 24 months

End point title	Clinical remission 24 months
End point description: The primary efficacy endpoints were the proportion of patients achieving at 3 and 24 months, at least 8 consecutive weeks of clinical remission (CR), defined as a clinical SLEDAI-2K=0, where serology was	

permitted (maximum SLEDAI=4) following the later Zen et al equivalent definition, in the absence of any BILAG A, B or C score.

End point type	Primary
End point timeframe:	
24 months	

End point values	Azathioprine	Mycophenolate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	118		
Units: percent				
number (not applicable)	48.3	71.2		

### Statistical analyses

Statistical analysis title	SLEDAI 24 months
Comparison groups	Azathioprine v Mycophenolate
Number of subjects included in analysis	236
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	t-test, 2-sided

### Secondary: BILAG A/B flares

End point title	BILAG A/B flares
End point description:	
Flares according to BILAG (British Isles Lupus Assessment Group) scores	
End point type	Secondary
End point timeframe:	
24 months	

End point values	Azathioprine	Mycophenolate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	120		
Units: percent				
number (not applicable)	71.7	50		

### Statistical analyses



<b>Statistical analysis title</b>	BILAG flares
Comparison groups	Mycophenolate v Azathioprine
Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	t-test, 2-sided

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### Secondary: Corticosteroids use reduction

End point title	Corticosteroids use reduction
End point description: Reduction of the prednisone dose (<7.5) by month 24 among those patients taking ≥7.5mg/day at inclusion	
End point type	Secondary
End point timeframe: 24 months	

<b>End point values</b>	Azathioprine	Mycophenolate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	120		
Units: percent				
number (not applicable)	83.5	94.9		

### Statistical analyses

<b>Statistical analysis title</b>	Corticosteroids use
Comparison groups	Azathioprine v Mycophenolate
Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.027
Method	t-test, 2-sided

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

24 months

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	12
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### Reporting groups

Reporting group title	AZA group
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Reporting group description: -

Reporting group title	EC-MPS
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Reporting group description: -

Serious adverse events	AZA group	EC-MPS	
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 120 (10.83%)	11 / 120 (9.17%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	1	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Thymoma			
subjects affected / exposed	1 / 120 (0.83%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	2 / 120 (1.67%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervix carcinoma			
subjects affected / exposed	0 / 120 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			

subjects affected / exposed	1 / 120 (0.83%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiovascular disorder			
subjects affected / exposed	1 / 120 (0.83%)	3 / 120 (2.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Subarachnoid haematoma			
subjects affected / exposed	0 / 120 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonia			
subjects affected / exposed	3 / 120 (2.50%)	5 / 120 (4.17%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 1	
Renal and urinary disorders			
Pyelonephritis			
subjects affected / exposed	2 / 120 (1.67%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Soft tissue infection			
subjects affected / exposed	2 / 120 (1.67%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 2	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	AZA group	EC-MPS	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	69 / 120 (57.50%)	71 / 120 (59.17%)	
General disorders and administration site conditions			

No specified subjects affected / exposed occurrences (all)	19 / 120 (15.83%) 19	28 / 120 (23.33%) 28	
Immune system disorders			
Pneumonia subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1	3 / 120 (2.50%) 3	
Oral candidiasis subjects affected / exposed occurrences (all)	2 / 120 (1.67%) 2	1 / 120 (0.83%) 1	
Leucopenia subjects affected / exposed occurrences (all)	5 / 120 (4.17%) 5	0 / 120 (0.00%) 0	
Gastrointestinal disorders			
Upper gastrointestinal symptoms subjects affected / exposed occurrences (all)	16 / 120 (13.33%) 16	9 / 120 (7.50%) 9	
Hepatobiliary disorders			
Liver toxicity subjects affected / exposed occurrences (all)	3 / 120 (2.50%) 3	0 / 120 (0.00%) 0	
Infections and infestations			
Upper respiratory tract infection subjects affected / exposed occurrences (all)	12 / 120 (10.00%) 12	16 / 120 (13.33%) 16	
Urinary tract infection subjects affected / exposed occurrences (all)	4 / 120 (3.33%) 4	4 / 120 (3.33%) 4	
Herpes sepsis subjects affected / exposed occurrences (all)	3 / 120 (2.50%) 3	5 / 120 (4.17%) 5	
Soft tissue infection subjects affected / exposed occurrences (all)	2 / 120 (1.67%) 2	2 / 120 (1.67%) 2	
Influenza subjects affected / exposed occurrences (all)	2 / 120 (1.67%) 2	3 / 120 (2.50%) 3	



## 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.

It was not a multiethnic study. Open-label and not double-blinded trial. Measures of active metabolites of AZA or EC-MPS) were not routinely performed. Corticosteroids were not adjusted during the study. Long-term potential outcomes not considered.
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Notes:

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/28450313>