Clinical trial results:
A multicentre study to assess the safety and efficacy of sodium hyaluronate (Hyalgan-F) produced by fermentation in knee psteoarthritis.

Summary

EudraCT number	2005-002735-27
Trial protocol	LV
Global end of trial date	13 June 2006

Results information

Result version number	v2 (current)
This version publication date	06 July 2022
First version publication date	02 April 2022
Version creation reason	• Correction of full data set I should add the data from secondary endpoint

Trial information

Trial identification

Sponsor protocol code	R30-05-01

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Fidia Farmaceutici S.p.A
Sponsor organisation address	Via Ponte della Fabbrica 3/A, Abano Terme, Italy, 35031
Public contact	Lucia Beinat, Fidia Farmaceutici S.p.A, +39 049 8232512, lbeinat@fidiapharma.it
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Sponsor organisation name	Fidia Farmaceutici S.p.A
Sponsor organisation address	Via Ponte della Fabbrica 3/A, Abano Terme, Italy, 35031
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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	13 June 2006
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 June 2006
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the potential immunogenicity of Hyalgan-F (HA-F) a sodium hyaluronate obtained by fermentation and administered by intra-articular (i.a.) route (5 i.a., once a wek for 5 weeks) in a patients with knee osteoarthritis (OA).

Protection of trial subjects:

Females of child-bearing potential (i.e. not in menopausal status from at least one year or permanently sterilized) had to have a negative urine pregnancy test prior to the first investigational medicinal product (IMP) administration

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 September 2005
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	5 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Latvia: 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)	120
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

- Patients of both genders, ambulant, aged ≥ 40 years, with primary knee OA associated with moderate to severe knee pain.
- Diagnosis of OA of the knee according to ACRC.
- OA of KL grade II – III
- At baseline VAS pain score ≥ 40 mm
- Analgesic/NSAID therapy was discontinued if previously taken prior to baseline

Pre-assignment period milestones

Number of subjects started	120
Number of subjects completed	120

Period 1

Period 1 title	Hyalgan-F (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Hyalgan-F (HA-F)

Arm description:

Patients were treated with five i.a. injections of HA-F 2 ml, one injection a week for five weeks, starting from baseline [week 0]) up to six months of follow-up with clinical visits and evaluations.

Arm type	One arm
Investigational medicinal product name	Hyalgan-F
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion in pre-filled syringe
Routes of administration	Intraarticular use

Dosage and administration details:

Hyalgan-F 20mg/2ml

Sodium Hyaluronate	20 mg
Sodium chloride	17 mg
Monobasic sodium phosphate	0.1 mg
Dibasic sodium phosphate	1.2 mg
Water for injection q.s. to	2 ml

Number of subjects in period 1	Hyalgan-F (HA-F)
Started	120
Completed	117
Not completed	3
Adverse event, serious fatal	1

Did not meet inclusion criteria	1
Lost to follow-up	1

Baseline characteristics

Reporting groups

Reporting group title	Hyalgan-F

Reporting group description: -

Reporting group values	Hyalgan-F	Total	
Number of subjects	120	120	
Age categorical Units: Subjects			
Adults (18-64 years)	120	120	
Gender categorical Units: Subjects			
Female	103	103	
Male	17	17	

Subject analysis sets

Subject analysis set title	mITT 35 days
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The Modified Intention to Treat population (ITT) was defined as all patients who received at least one dose of the study drug with at least one post-treatment immunological data, and was used for all the immunological and efficacy analyses.

Subject analysis set title	mITT 60 days
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The Modified Intention to Treat population (ITT) was defined as all patients who received at least one dose of the study drug with at least one post-treatment immunological data, and was used for all the immunological and efficacy analyses.

Subject analysis set title	mITT-120 days
Subject analysis set type	Safety analysis

Subject analysis set description:

The Modified Intention to Treat population (ITT) was defined as all patients who received at least one dose of the study drug with at least one post-treatment immunological data, and was used for all the immunological and efficacy analyses.

Subject analysis set title	mITT-180 days
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The Modified Intention to Treat population (ITT) was defined as all patients who received at least one dose of the study drug with at least one post-treatment immunological data, and was used for all the immunological and efficacy analyses.

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety population was defined as all patients who received at least one dose of study drug and was used for all safety analyses including demographic data, AEs, laboratory data and vital signs.

Reporting group values	mITT 35 days	mITT 60 days	mITT-120 days
Number of subjects	119	118	118
Age categorical Units: Subjects			
Adults (18-64 years)	119	118	118
Gender categorical Units: Subjects			
Female			
Male			

Reporting group values	mITT-180 days	Safety Population	
Number of subjects	117	120	
Age categorical Units: Subjects			
Adults (18-64 years)	117	120	
Gender categorical Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	Hyalgan-F (HA-F)

Reporting group description:

Patients were treated with five i.a. injections of HA-F 2 ml, one injection a week for five weeks, starting from baseline [week 0]) up to six months of follow-up with clinical visits and evaluations.

Subject analysis set title	mITT 35 days
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The Modified Intention to Treat population (ITT) was defined as all patients who received at least one dose of the study drug with at least one post-treatment immunological data, and was used for all the immunological and efficacy analyses.

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Subject analysis set type	Safety analysis

Subject analysis set description:

The Modified Intention to Treat population (ITT) was defined as all patients who received at least one dose of the study drug with at least one post-treatment immunological data, and was used for all the immunological and efficacy analyses.

Subject analysis set title	mITT-180 days
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The Modified Intention to Treat population (ITT) was defined as all patients who received at least one dose of the study drug with at least one post-treatment immunological data, and was used for all the immunological and efficacy analyses.

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety population was defined as all patients who received at least one dose of study drug and was used for all safety analyses including demographic data, AEs, laboratory data and vital signs.

Primary: Incidence of Immunogenic response of HA-F

End point title	Incidence of Immunogenic response of HA-F[1]

End point description:

End point type	Primary

End point timeframe:

The incidence of positive immunogenic response to HA-F calculated at 35 days and 60 days after treatment among patients with a negative immunogenic response at baseline

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis were performed

End point values	mITT 35 days	mITT 60 days		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	118	117		
Units: percentage protection				
number (confidence interval 95%)	99.2 (97 to 100)	98.3 (97 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy measured in VAS scale

End point title	Efficacy measured in VAS scale

End point description:

Results were summarized descriptively for each visit (Day 0, Day 35, Day 60, Day 120, and Day 180). The change from baseline was analyzed and the corresponding 95% CIs were presented. P-values were obtained from a two-sided test of the null-hypothesis that the change from baseline was zero. The time taken to perform the 50 ft walking test was also reported.

End point type	Secondary

End point timeframe:

The VAS was evaluated at baseline, Day 35, Day 60, Day 120 and Day 180.

End point values	Hyalgan-F (HA-F)	mITT 35 days	mITT 60 days	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	119	119	118	
Units: millimetre(s)				
median (full range (min-max))	60.5 (40 to 91)	-29 (-82 to 14)	-41.0 (-91 to 19)	

Statistical analyses

No statistical analyses for this end point

Secondary: WOMAC index assessment-Pain

End point title	WOMAC index assessment-Pain

End point description:

Results were summarized descriptively for each visit (Day 0, Day 35, Day 60, Day 120, and Day 180). The change from baseline was analyzed and the corresponding 95% CIs were presented. P-values were obtained from a two-sided test of the null-hypothesis that the change from baseline was zero. The time taken to perform the 50 ft walking test was also reported.

End point type	Secondary

End point timeframe:

The WOMAC was measured at baseline, Day 35, Day 60, Day 120, and Day 180.

End point values	Hyalgan-F (HA-F)	mITT 35 days	mITT 60 days	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	119	119	118	
Units: millimiter				
median (full range (min-max))	213.0 (32 to 445)	122.0 (1 to 335)	86.5 (0 to 437)	

Statistical analyses

No statistical analyses for this end point

Secondary: WOMAC index assessment-Stifness

End point title	WOMAC index assessment-Stifness

End point description:

End point type	Secondary

End point timeframe:

Day 0, 35, 60, 120, 180

End point values	Hyalgan-F (HA-F)	mITT 35 days	mITT 60 days	mITT-120 days
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	119	119	118	118
Units: millimiters				
median (full range (min-max))	101.0 (2 to 185)	60.0 (0 to 164)	44.5 (0 to 177)	45.0 (0 to 159)

End point values	mITT-180 days			
Subject group type	Subject analysis set			
Number of subjects analysed	117			
Units: millimiters				
median (full range (min-max))	47.0 (0 to 187)			

Statistical analyses

No statistical analyses for this end point

Secondary: WOMAC index assessment-Function

End point title	WOMAC index assessment-Function

End point description:

End point type	Secondary

End point timeframe:

Day 0, 35, 60, 120, 180

End point values	Hyalgan-F (HA-F)	mITT 35 days	mITT 60 days	mITT-120 days
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	119	119	118	118
Units: millimiters				
median (full range (min-max))	854 (100 to 1529)	530.0 (10 to 1359)	384.5 (7 to 1535)	390 (2 to 1330)

End point values	mITT-180 days			
Subject group type	Subject analysis set			
Number of subjects analysed	117			
Units: millimiters				
median (full range (min-max))	411.0 (0 to 1405)			

Statistical analyses

No statistical analyses for this end point

Secondary: Immunological Parameters-C3

End point title	Immunological Parameters-C3

End point description:

End point type	Secondary

End point timeframe:

Day 0, 35 and 60

End point values	Hyalgan-F (HA-F)	mITT 35 days	mITT 60 days	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	119	119	118	
Units: mg/dL				
median (full range (min-max))	124.0 (38 to 180)	124.0 (71 to 179)	120.0 (67 to 199)	

Statistical analyses

No statistical analyses for this end point

Secondary: Immunological Parameters-C4

End point title	Immunological Parameters-C4

End point description:

End point type	Secondary

End point timeframe:

Day 0, 35, 60

End point values	Hyalgan-F (HA-F)	mITT 35 days	mITT 60 days	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	119	119	118	
Units: mg/dL				
median (full range (min-max))	28.0 (7 to 59)	28 (11 to 57)	29.0 (15 to 55)	

Statistical analyses

No statistical analyses for this end point

Secondary: Immunological Parameters-AH50

End point title	Immunological Parameters-AH50

End point description:

End point type	Secondary

End point timeframe:

Day 0, 35, 60

End point values	Hyalgan-F (HA-F)	mITT 35 days	mITT 60 days	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	118	119	118	
Units: U/mL				
median (full range (min-max))	114.0 (70 to 176)	105.0 (50 to 160)	108.5 (54 to 177)	

Statistical analyses

No statistical analyses for this end point

Secondary: Immunological Parameters-CH50

End point title	Immunological Parameters-CH50

End point description:

End point type	Secondary

End point timeframe:

day 0, 35, 60

End point values	Hyalgan-F (HA-F)	mITT 35 days	mITT 60 days	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	118	119	118	
Units: U/mL				
median (full range (min-max))	300 (0 to 453)	304.0 (0 to 436)	308.0 (161 to 442)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The time period for recording AE was from Baseline V2 Day 0 to V10 Day 180

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	8.2

Reporting groups

Reporting group title	Hyalgan-F

Reporting group description: -

Serious adverse events	Hyalgan-F		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 120 (2.50%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
Reproductive system and breast disorders			
Ovarian cyst, Peritonitis, Jejunal perforatio,			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Respiratory, thoracic and mediastinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Herpes zoster			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Hyalgan-F		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 120 (23.33%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	26 / 120 (21.67%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Joint effusion			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Arthralgia			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Osteoarthritis			
subjects affected / exposed	12 / 120 (10.00%)		
occurrences (all)	12		
Infections and infestations			
Influenza			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Respiratory tract infection			
subjects affected / exposed	5 / 120 (4.17%)		
occurrences (all)	5		

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

None reported