Clinical trial results:
Phase II clinical trial to know the effectiveness and safety with a treatment based in a therapy with serical autologous white cells versus the use of platelet rich plasma in patients with rotulian and achilles tendinopathy

Summary

EudraCT number	2017-002129-39
Trial protocol	ES
Global end of trial date	22 March 2021

Results information

Result version number	v1 (current)
This version publication date	15 June 2022
First version publication date	15 June 2022

Trial information

Trial identification

Sponsor protocol code	XC.ROD.2017

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	XCELL Medical Solutions SL
Sponsor organisation address	C/ Fortuny, N.º 29, Piso 1º, Madrid, Spain, 28010
Public contact	Pablo García de la Riva, XCELL Medical Solutions SL, 34 620340632, pgdelariva@m2rlab.com
Scientific contact	Pablo García de la Riva, XCELL Medical Solutions SL, 34 620340632, pgdelariva@m2rlab.com

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	28 April 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 March 2021
Global end of trial reached?	Yes
Global end of trial date	22 March 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluate and compare the effectiveness in pain reduction and safety in a treatment based in a therapy with serical autologous white cells versus the use of platelet rich plasma with the commercial kit of GPS® III from Biomet Biologics.

Protection of trial subjects:

The study was in compliance with ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy:

At the start of the study, the patients continued with the medications prescribed by their doctor. After the infiltrations, the patients were able to take paracetamol or opioid analgesics at standard doses in case of unbearable local pain. After 48 hours following each of the infiltrations, local cryotherapy can be used.

Evidence for comparator:

The administration of the study treatment and its comparator were done in the same way using the same type of material.

Actual start date of recruitment	28 October 2019
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 48
Worldwide total number of subjects	48
EEA total number of subjects	48

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	47
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

48 patients who met the selection criteria were recruited for the study from October 28, 2019 to October 7, 2020. 8 patients were excluded due to screening failure (4), patient decision (3) and adverse event before treatment (1). Thus, 40 patients were randomized and all of them completed the study.

Pre-assignment

Screening details:

The principal investigator selected among the cases that came to his consultation, those that fit the patient profile defined by the selection criteria and that agreed to participate in the trial.

Period 1

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

Blinding implementation details:

The treatment was administered by a person other than the evaluator.

Arms

Are arms mutually exclusive?	Yes
Arm title	XCell (Treatment)

Arm description:

Autologous serum therapy with white blood cells (M2R-XCell)

Arm type	Experimental
Investigational medicinal product name	Autologous serum therapy with white blood cells (M2R-XCell)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Infiltration

Dosage and administration details:

Patellar tendon infiltration: It was injected by local intratendinous infiltration with a 21G needle. The doctor was guided by ultrasound to put the product in the damaged area. Depending on the extent of the lesion, between 4 and 8 cc. It was injected following the longitudinal axis of the tendon, from caudal to cephalad. To reach the most posterior area of the tendon, infiltration was performed along the axial axis from the lateral to the medial aspect of the knee.

Achilles tendon infiltration: It was injected by local intratendinous infiltration with a 21G needle. The doctor was guided by ultrasound to put the product in the damaged area. Depending on the extent of the lesion, between 3 and 5 cc. It was injected following the longitudinal axis of the tendon, from cephalic to caudal. The "peppering" technique was used, which consists of inserting the needle into the tendon, injecting part of the product, withdrawing without leaving the skin, redirecting and reinserting to deposi

Arm title	PRP (Control)

Arm description:

Platelet Rich Plasma (PRP) with Biomet Biologics GPS® III Commercial Kit

Arm type	Active comparator
Investigational medicinal product name	Platelet Rich Plasma (PRP) with Biomet Biologics GPS® III Commercial Kit
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Injection , Infiltration

Dosage and administration details:

Patellar tendon infiltration: It was injected by local intratendinous infiltration with a 21G needle. The doctor was guided by ultrasound to put the product in the damaged area. Depending on the extent of the lesion, between 4 and 8 cc. It was injected following the longitudinal axis of the tendon, from caudal to cephalad. To reach the most posterior area of the tendon, infiltration was performed along the axial axis from the lateral to the medial aspect of the knee.

Achilles tendon infiltration: It was injected by local intratendinous infiltration with a 21G needle. The doctor was guided by ultrasound to put the product in the damaged area. Depending on the extent of the lesion, between 3 and 5 cc. It was injected following the longitudinal axis of the tendon, from cephalic to caudal. The "peppering" technique was used, which consists of inserting the needle into the tendon, injecting part of the product, withdrawing without leaving the skin, redirecting and reinserting to deposi

Number of subjects in period 1[1]	XCell (Treatment)	PRP (Control)
Started	20	20
Completed	20	20

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 48 patients were recruited for the study from October 28, 2019 to October 7, 2020. Of the 48 patients, 8 were excluded due to screening failure (4), patient decision (3) and adverse event before treatment (one). Therefore, 40 patients were randomized and treated.

Baseline characteristics

Reporting groups	
Reporting group title	XCell (Treatment)
Reporting group description:	
Autologous serum therapy with white blood cells (M2R-XCell)	
Reporting group title	PRP (Control)
Reporting group description:	
Platelet Rich Plasma (PRP) with Biomet Biologics GPS® III Commercial Kit	

Reporting group values	XCell (Treatment)	PRP (Control)	Total
Number of subjects	20	20	40
Age categorical Units: Subjects			
Adults (18-64 years)	19	20	39
From 65-84 years	1	0	1
Age continuous Units: years			
arithmetic mean	49.3	49.5	
standard deviation	± 12.9	± 7.6	-
Gender categorical Units: Subjects			
Female	7	6	13
Male	13	14	27
Activity level Units: Subjects			
Professional	18	15	33
Amateur	2	5	7
Injured tendon Units: Subjects			
Patellar	4	1	5
Achilles	16	19	35
Dominant leg Units: Subjects			
Right	13	15	28
Left	7	4	11
Ambidextrous	0	1	1
Laterality of the lesion Units: Subjects			
Right	13	7	20
Left	7	13	20
Previous treatment with PRP			
PRP, Platelet Rich Plasma			
Units: Subjects			
Yes	0	2	2
No	20	18	38
Neovascularization Units: Subjects			

Yes	9	7	16
No	11	13	24

VISA			
Patellar tendinopathy severity index (VISA-P) or Achilles tendinopathy (VISA-A) to analyze the evolution of pain and the degree of severity of the injury. The Victorian Institute of Sport Assessment (VISA) scale allows a clinical classification based on symptom severity, functional capacity and sports capacity. The VISA questionnaire score ranges on a scale of 0 to 100, where the higher the score, the better the condition of the tendon.			
Units: points			
arithmetic mean	50.7	55.1	
standard deviation	± 18.6	± 14.3	-
VAS			
VAS, subjective pain scale. The VAS score ranges on a scale from 0 to 10, with a higher score greater pain.			
Units: points			
arithmetic mean	4.9	4.9	
standard deviation	± 2.2	± 1.5	-
Cincinnati function scale			
Sports assessment instrument: the Cincinnati Sports Activity Scale (CSAS). The Cincinnati questionnaire score ranges from 0 to 100, where the higher the score, the better the functionality.			
Units: points			
arithmetic mean	56.3	57.6	
standard deviation	± 14.5	± 11.9	-
Weight			
Units: kilogram(s)			
arithmetic mean	79.7	83.1	
standard deviation	± 17.4	± 15.7	-
Height			
Units: points			
arithmetic mean	174.0	174.6	
standard deviation	± 11.6	± 10.2	-
BMI			
BMI, Body mass index			
Units: kilogram(s)/square metre			
arithmetic mean	26.1	27.1	
standard deviation	± 3.7	± 3.6	-
Goniometry - Internal Rotation			
Units: degree			
arithmetic mean	20.8	23.3	
standard deviation	± 13.0	± 9.9	-
Goniometry - External Rotation			
Units: degree			
arithmetic mean	9.5	11.8	
standard deviation	± 6.1	± 5.7	-
Goniometry - Flexion			
Units: degree			
arithmetic mean	78.3	66.3	
standard deviation	± 34.5	± 24.4	-
Goniometry - Extension			
Units: degree			
arithmetic mean	10.5	12.0	
standard deviation	± 13.9	± 8.3	-

Ultrasound - Tendon thickness			
Units: centimetre			
arithmetic mean	8.9	8.4	
standard deviation	± 2.7	± 3.2	-
Ultrasound - Section area			
Units: square centimetre			
arithmetic mean	5.6	9.7	
standard deviation	± 6.6	± 20.9	-
Ultrasound - Thickness of the tendon at 1 cm from the point of insertion			
Units: degree			
arithmetic mean	4.0	4.1	
standard deviation	± 2.4	± 1.1	-
Ultrasound - Difference in thicknesses			
Units: degree			
arithmetic mean	4.9	4.3	
standard deviation	± 3.3	± 3.3	-

End points

End points reporting groups

Reporting group title	XCell (Treatment)
Reporting group description:	
Autologous serum therapy with white blood cells (M2R-XCell)	
Reporting group title	PRP (Control)
Reporting group description:	
Platelet Rich Plasma (PRP) with Biomet Biologics GPS® III Commercial Kit	

Primary: Change in VISA questionnaire score at 24 weeks after treatment

End point title	Change in VISA questionnaire score at 24 weeks after treatment
End point description:	
Patellar tendinopathy severity index (VISA-P) or Achilles tendinopathy (VISA-A) to analyze the evolution of pain and the degree of severity of the injury. The Victorian Institute of Sport Assessment (VISA) scale allows a clinical classification based on symptom severity, functional capacity and sports capacity. The VISA questionnaire score ranges on a scale of 0 to 100, where the higher the score, the better the condition of the tendon.	
End point type	Primary
End point timeframe:	
Difference from baseline to 24 weeks after treatment	

End point values	XCell (Treatment)	PRP (Control)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: Points				
arithmetic mean (standard deviation)	24.8 (± 22.7)	22.8 (± 19.8)		

Statistical analyses

Statistical analysis title	Differences between groups
Statistical analysis description:	
Difference in VISA questionnaire from baseline to 24 weeks after treatment. Student's t-test was used to assess potential differences between treatment groups.	
Comparison groups	XCell (Treatment) v PRP (Control)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.842
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	1.95

Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.6
upper limit	13.5

Statistical analysis title	Change from baseline to 24 week in XCell group

Statistical analysis description:

Difference in VISA questionnaire from baseline to 24 weeks after treatment in XCell group. Student's t-test was used to assess potential differences between treatment groups.

Comparison groups	XCell (Treatment) v PRP (Control)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	24.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	14.1
upper limit	35.4
Variability estimate	Standard deviation
Dispersion value	22.7

Statistical analysis title	Change from baseline to 24 week in PRP group

Statistical analysis description:

Difference in VISA questionnaire from baseline to 24 weeks after treatment in PRP group. Student's t-test was used to assess potential differences between treatment groups.

Comparison groups	PRP (Control) v XCell (Treatment)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	22.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	13.5
upper limit	32.1
Variability estimate	Standard deviation
Dispersion value	19.8

Primary: Change in VAS questionnaire score at 24 weeks after treatment	
End point title	Change in VAS questionnaire score at 24 weeks after treatment
End point description:	
VAS, subjective pain scale. The VAS score ranges on a scale from 0 to 10, with a higher score greater pain.	
End point type	Primary
End point timeframe:	
Difference from baseline to 24 weeks after treatment	

End point values	XCell (Treatment)	PRP (Control)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: Points				
arithmetic mean (standard deviation)	-3.4 (± 2.6)	-3.7 (± 1.7)		

Statistical analyses

Statistical analysis title	Differences between groups
Statistical analysis description:	
Difference in VAS scale from baseline to 24 weeks after treatment. Student's t-test was used to assess potential differences between treatment groups.	

Comparison groups	XCell (Treatment) v PRP (Control)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.381
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	1.3

Statistical analysis title	Change from baseline to 24 week in XCell group
Statistical analysis description:	
Difference in VAS scale from baseline to 24 weeks after treatment in XCell group. Student's t-test was used to assess potential differences between treatment groups.	

Comparison groups	XCell (Treatment) v PRP (Control)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	-3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.6
upper limit	-2.2
Variability estimate	Standard deviation
Dispersion value	2.6

Statistical analysis title	Change from baseline to 24 week in PRP group

Statistical analysis description:

Difference in VAS scale from baseline to 24 weeks after treatment in PRP group. Student's t-test was used to assess potential differences between treatment groups.

Comparison groups	PRP (Control) v XCell (Treatment)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-3.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.5
upper limit	-2.9
Variability estimate	Standard deviation
Dispersion value	1.7

Secondary: Change in Cincinnati Function Scale (CSAS) at 24 weeks after treatment

End point title	Change in Cincinnati Function Scale (CSAS) at 24 weeks after treatment

End point description:

End point type	Secondary

End point timeframe:

Difference from baseline to 24 weeks after treatment

End point values	XCell (Treatment)	PRP (Control)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: Points				
arithmetic mean (standard deviation)	28.8 (± 15.1)	32.4 (± 15.7)		

Statistical analyses

Statistical analysis title	Differences between groups

Statistical analysis description:

Difference in Cincinnati Function Scale (CSAS) from baseline to 24 weeks after treatment. Student's t-test was used to assess potential differences between treatment groups.

Comparison groups	XCell (Treatment) v PRP (Control)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.259
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-3.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.7
upper limit	4.4

Statistical analysis title	Change from baseline to 24 week in XCell group

Statistical analysis description:

Difference in Cincinnati Function Scale (CSAS) from baseline to 24 weeks after treatment in XCell group. Student's t-test was used to assess potential differences between treatment groups.

Comparison groups	XCell (Treatment) v PRP (Control)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Median difference (final values)
Point estimate	28.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	21.7
upper limit	35.8
Variability estimate	Standard deviation
Dispersion value	15.1

Statistical analysis title	Change from baseline to 24 week in PRP group

Statistical analysis description:

Difference in Cincinnati Function Scale (CSAS) from baseline to 24 weeks after treatment in PRP group. Student's t-test was used to assess potential differences between treatment groups.

Comparison groups	PRP (Control) v XCell (Treatment)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	32.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	25.1
upper limit	39.7
Variability estimate	Standard deviation
Dispersion value	15.7

Secondary: Time to return to regular physical activity at 24 weeks after treatment

End point title	Time to return to regular physical activity at 24 weeks after treatment

End point description:

End point type	Secondary

End point timeframe:

Difference from baseline to 24 weeks after treatment

End point values	XCell (Treatment)	PRP (Control)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	18		
Units: day				
arithmetic mean (standard deviation)	60.3 (± 60.0)	38.2 (± 25.4)		

Statistical analyses

Statistical analysis title	Differences between groups

Statistical analysis description:

Differences in time to return to regular physical activity from baseline to 24 weeks after treatment. Student's t-test was used to assess potential differences between treatment groups.

Comparison groups	XCell (Treatment) v PRP (Control)
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.558
Method	t-test, 2-sided

Secondary: Ultrasound evolution (tendon thickness) at 24 weeks after treatment

End point title	Ultrasound evolution (tendon thickness) at 24 weeks after treatment

End point description:

End point type	Secondary

End point timeframe:

Difference from baseline to 24 weeks after treatment

End point values	XCell (Treatment)	PRP (Control)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: centimetre				
arithmetic mean (standard deviation)	-1.3 (± 1.2)	-1.3 (± 1.9)		

Statistical analyses

Statistical analysis title	Differences between groups

Statistical analysis description:

Differences in tendon thickness (cm) from baseline to 24 weeks after treatment. Student's t-test was used to assess potential differences between treatment groups.

Comparison groups	XCell (Treatment) v PRP (Control)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.836
Method	t-test, 2-sided

Statistical analysis title	Change from baseline to 24 week in XCell group
Statistical analysis description:	
Differences in tendon thickness (cm) from baseline to 24 weeks after treatment in XCell group. Student's t-test was used to assess potential differences between treatment groups.	
Comparison groups	XCell (Treatment) v PRP (Control)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	-0.8
Variability estimate	Standard deviation
Dispersion value	1.2

Statistical analysis title	Change from baseline to 24 week in PRP group
Statistical analysis description:	
Differences in tendon thickness (cm) from baseline to 24 weeks after treatment in PRP group. Student's t-test was used to assess potential differences between treatment groups.	
Comparison groups	PRP (Control) v XCell (Treatment)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.009
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.2
upper limit	-0.3
Variability estimate	Standard deviation
Dispersion value	1.9

Secondary: Neovascularization at 24 weeks after treatment

End point title	Neovascularization at 24 weeks after treatment

End point description:

End point type	Secondary

End point timeframe:

Difference from baseline to 24 weeks after treatment

End point values	XCell (Treatment)	PRP (Control)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: Absolute frecuency				
Yes	8	8		
No	12	12		

Statistical analyses

Statistical analysis title	Change between baseline and 24 weeks of treatment

Statistical analysis description:

Differences in neovascularization from baseline to 24 weeks after treatment. Student's t-test was used to assess potential differences between treatment groups.

Comparison groups	XCell (Treatment) v PRP (Control)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	t-test, 2-sided

Secondary: Change in range of motion with goniometer (Internal Rotation) at 24 weeks after treatment

End point title	Change in range of motion with goniometer (Internal Rotation) at 24 weeks after treatment

End point description:

End point type	Secondary

End point timeframe:

Difference from baseline to 24 weeks after treatment

End point values	XCell (Treatment)	PRP (Control)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: degree				
arithmetic mean (standard deviation)	-0.8 (± 6.9)	-0.5 (± 4.8)		

Statistical analyses

Statistical analysis title	Differences between groups
Statistical analysis description:	
Differences in internal rotation measured by the goniometer from baseline to 24 weeks after treatment. Student's t-test was used to assess potential differences between treatment groups.	
Comparison groups	XCell (Treatment) v PRP (Control)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.448
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.7
upper limit	3.2

Statistical analysis title	Change from baseline to 24 week in XCell group
Statistical analysis description:	
Differences in internal rotation measured by the goniometer from baseline to 24 weeks after treatment in XCell group. Student's t-test was used to assess potential differences between treatment groups.	
Comparison groups	XCell (Treatment) v PRP (Control)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4
upper limit	2.5

Variability estimate	Standard deviation
Dispersion value	6.9

Statistical analysis title	Change from baseline to 24 week in PRP group

Statistical analysis description:

Differences in internal rotation measured by the goniometer from baseline to 24 weeks after treatment in PRP group. Student's t-test was used to assess potential differences between treatment groups.

Comparison groups	PRP (Control) v XCell (Treatment)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.625
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.8
upper limit	1.8
Variability estimate	Standard deviation
Dispersion value	4.8

Secondary: Change in range of motion with goniometer (External Rotation) at 24 weeks after treatment

End point title	Change in range of motion with goniometer (External Rotation) at 24 weeks after treatment

End point description:

End point type	Secondary

End point timeframe:

Difference from baseline to 24 weeks after treatment

End point values	XCell (Treatment)	PRP (Control)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: degree				
arithmetic mean (standard deviation)	1.0 (± 3.1)	-0.5 (± 3.6)		

Statistical analyses

Statistical analysis title	Differences between groups
Statistical analysis description:	
Differences in external rotation measured by the goniometer from baseline to 24 weeks after treatment. Student's t-test was used to assess potential differences between treatment groups.	
Comparison groups	XCell (Treatment) v PRP (Control)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.52
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	3.6

Statistical analysis title	Change from baseline to 24 week in XCell group
Statistical analysis description:	
Differences in external rotation measured by the goniometer from baseline to 24 weeks after treatment in XCell group. Student's t-test was used to assess potential differences between treatment groups.	
Comparison groups	XCell (Treatment) v PRP (Control)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	2.4
Variability estimate	Standard deviation
Dispersion value	3.1

Statistical analysis title	Change from baseline to 24 week in PRP group
Statistical analysis description:	
Differences in external rotation measured by the goniometer from baseline to 24 weeks after treatment in PRP group. Student's t-test was used to assess potential differences between treatment groups.	
Comparison groups	PRP (Control) v XCell (Treatment)

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.2
upper limit	1.2
Variability estimate	Standard deviation
Dispersion value	3.6

Secondary: Change in range of motion with goniometer (Flexion) at 24 weeks after treatment

End point title	Change in range of motion with goniometer (Flexion) at 24 weeks after treatment

End point description:

End point type	Secondary

End point timeframe:

Difference from baseline to 24 weeks after treatment

End point values	XCell (Treatment)	PRP (Control)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: degree				
arithmetic mean (standard deviation)	7.5 (± 13.5)	9.0 (± 19.9)		

Statistical analyses

Statistical analysis title	Differences between groups

Statistical analysis description:

Differences in flexion measured by the goniometer from baseline to 24 weeks after treatment. Student's t-test was used to assess potential differences between treatment groups.

Comparison groups	XCell (Treatment) v PRP (Control)

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.711
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11
upper limit	8

Statistical analysis title	Change from baseline to 24 week in XCell group

Statistical analysis description:

Differences in flexion measured by the goniometer from baseline to 24 weeks after treatment in XCell group. Student's t-test was used to assess potential differences between treatment groups.

Comparison groups	XCell (Treatment) v PRP (Control)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	7.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2
upper limit	13.8
Variability estimate	Standard deviation
Dispersion value	13.5

Statistical analysis title	Change from baseline to 24 week in PRP group

Statistical analysis description:

Differences in flexion measured by the goniometer from baseline to 24 weeks after treatment in PRP group. Student's t-test was used to assess potential differences between treatment groups.

Comparison groups	XCell (Treatment) v PRP (Control)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.058
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	9

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	18.3
Variability estimate	Standard deviation
Dispersion value	19.9

Secondary: Change in range of motion with goniometer (Extension) at 24 weeks after treatment

End point title	Change in range of motion with goniometer (Extension) at 24 weeks after treatment

End point description:

End point type	Secondary

End point timeframe:

Difference from baseline to 24 weeks after treatment

End point values	XCell (Treatment)	PRP (Control)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: degree				
arithmetic mean (standard deviation)	0.4 (± 12.7)	0.0 (± 7.4)		

Statistical analyses

Statistical analysis title	Differences between groups

Statistical analysis description:

Differences in extension measured by the goniometer from baseline to 24 weeks after treatment. Student's t-test was used to assess potential differences between treatment groups.

Comparison groups	XCell (Treatment) v PRP (Control)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.482
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	4

Statistical analysis title	Change from baseline to 24 week in XCell group
Statistical analysis description:	
Differences in extension measured by the goniometer from baseline to 24 weeks after treatment in XCell group. Student's t-test was used to assess potential differences between treatment groups.	
Comparison groups	XCell (Treatment) v PRP (Control)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.075
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.5
upper limit	6.3
Variability estimate	Standard deviation
Dispersion value	12.7

Statistical analysis title	Change from baseline to 24 week in PRP group
Statistical analysis description:	
Differences in extension measured by the goniometer from baseline to 24 weeks after treatment in PRP group. Student's t-test was used to assess potential differences between treatment groups.	
Comparison groups	PRP (Control) v XCell (Treatment)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.951
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.5
upper limit	3.5
Variability estimate	Standard deviation
Dispersion value	7.4

Secondary: Ultrasound evolution (section area) at 24 weeks after treatment	
End point title	Ultrasound evolution (section area) at 24 weeks after treatment

End point description:

End point type	Secondary

End point timeframe:

Difference from baseline to 24 weeks after treatment

End point values	XCell (Treatment)	PRP (Control)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: square centimetre				
arithmetic mean (standard deviation)	-4.5 (± 6.5)	-4.0 (± 6.5)		

Statistical analyses

Statistical analysis title	Differences between groups

Statistical analysis description:

Differences in section area (cm2) from baseline to 24 weeks after treatment. Student's t-test was used to assess potential differences between treatment groups.

Comparison groups	XCell (Treatment) v PRP (Control)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.55
Method	t-test, 2-sided

Statistical analysis title	Change from baseline to 24 week in XCell group

Statistical analysis description:

Differences in section area (cm2) from baseline to 24 weeks after treatment in XCell group. Student's t-test was used to assess potential differences between treatment groups.

Comparison groups	XCell (Treatment) v PRP (Control)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-4.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.5
upper limit	-1.4

Variability estimate	Standard deviation
Dispersion value	6.5

Statistical analysis title	Change from baseline to 24 week in PRP group

Statistical analysis description:

Differences in section area (cm2) from baseline to 24 weeks after treatment in PRP group. Student's t-test was used to assess potential differences between treatment groups.

Comparison groups	PRP (Control) v XCell (Treatment)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7
upper limit	-0.9
Variability estimate	Standard deviation
Dispersion value	6.5

Secondary: Ultrasound evolution (tendon thickness at 1 cm from the point of insertion) at 24 weeks after treatment

End point title	Ultrasound evolution (tendon thickness at 1 cm from the point of insertion) at 24 weeks after treatment

End point description:

End point type	Secondary

End point timeframe:

Difference from baseline to 24 weeks after treatment

End point values	XCell (Treatment)	PRP (Control)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: centimetre				
arithmetic mean (standard deviation)	-0.2 (± 1.8)	-0.3 (± 0.8)		

Statistical analyses

Statistical analysis title	Differences between groups

Statistical analysis description:

Differences in tendon thickness at 1 cm from the point of insertion (cm) from baseline to 24 weeks after treatment. Student's t-test was used to assess potential differences between treatment groups.

Comparison groups	XCell (Treatment) v PRP (Control)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.825
Method	t-test, 2-sided

Statistical analysis title	Change from baseline to 24 week in XCell group

Statistical analysis description:

Differences in tendon thickness at 1 cm from the point of insertion (cm) from baseline to 24 weeks after treatment in XCell group. Student's t-test was used to assess potential differences between treatment groups.

Comparison groups	XCell (Treatment) v PRP (Control)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.772
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0.6
Variability estimate	Standard deviation
Dispersion value	1.8

Statistical analysis title	Change from baseline to 24 week in PRP group

Statistical analysis description:

Differences in tendon thickness at 1 cm from the point of insertion (cm) from baseline to 24 weeks after treatment in PRP group. Student's t-test was used to assess potential differences between treatment groups.

Comparison groups	PRP (Control) v XCell (Treatment)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.19
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	0.1
Variability estimate	Standard deviation
Dispersion value	0.8

Secondary: Difference between the maximum thickness and the thickness of the tendon at 1 cm from the point of insertion at 24 weeks after treatment

End point title	Difference between the maximum thickness and the thickness of the tendon at 1 cm from the point of insertion at 24 weeks after treatment

End point description:

End point type	Secondary

End point timeframe:

Difference from baseline to 24 weeks after treatment

End point values	XCell (Treatment)	PRP (Control)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: centimetre				
arithmetic mean (standard deviation)	-1.1 (± 2.1)	-1.0 (± 1.9)		

Statistical analyses

Statistical analysis title	Differences between groups

Statistical analysis description:

Difference between the maximum thickness and the thickness of the tendon at 1 cm from the point of insertion (cm) from baseline to 24 weeks after treatment. Student's t-test was used to assess potential differences between treatment groups.

Comparison groups	XCell (Treatment) v PRP (Control)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.595
Method	t-test, 2-sided

Statistical analysis title	Change from baseline to 24 week in XCell group

Statistical analysis description:

Difference between the maximum thickness and the thickness of the tendon at 1 cm from the point of insertion from baseline to 24 weeks after treatment in XCell group. Student's t-test was used to assess potential differences between treatment groups.

Comparison groups	XCell (Treatment) v PRP (Control)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	-0.1
Variability estimate	Standard deviation
Dispersion value	2.1

Statistical analysis title	Change from baseline to 24 week in PRP group

Statistical analysis description:

Difference between the maximum thickness and the thickness of the tendon at 1 cm from the point of insertion from baseline to 24 weeks after treatment in PRP group. Student's t-test was used to assess potential differences between treatment groups.

Comparison groups	PRP (Control) v XCell (Treatment)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.029
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	-0.1
Variability estimate	Standard deviation
Dispersion value	1.9

Secondary: Satisfaction level at 24 weeks after treatment

End point title	Satisfaction level at 24 weeks after treatment

End point description:

End point type	Secondary

End point timeframe:

Difference from baseline to 24 weeks after treatment

End point values	XCell (Treatment)	PRP (Control)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: Absolute frecuency				
Poor	3	0		
Acceptable	3	5		
Good	8	11		
Excellent	6	4		

Statistical analyses

Statistical analysis title	Differences between groups

Statistical analysis description:

Differences in satisfacion level from baseline to 24 weeks after treatment. Student's t-test was used to assess potential differences between treatment groups.

Comparison groups	XCell (Treatment) v PRP (Control)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.267
Method	t-test, 2-sided

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Overall period, from 28/10/2019 to 22/03/2021	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0
Reporting groups	
Reporting group title	XCell (Treatment)
Reporting group description:	
Autologous serum therapy with white blood cells (M2R-XCell)	
Reporting group title	PRP (Control)
Reporting group description:	
Platelet Rich Plasma (PRP) with Biomet Biologics GPS® III Commercial Kit	

Serious adverse events	XCell (Treatment)	PRP (Control)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	XCell (Treatment)	PRP (Control)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
Musculoskeletal and connective tissue disorders			
Plantar fasciitis	Additional description: An adverse event occurred in a patient treated with PRP (5.0%). AE was plantar fasciitis in the left foot of mild intensity and unrelated to study treatment. The patient was left-handed and was treated for the Achilles tendon of the left foot.		
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 December 2017	Changes in the treatment part and addition of a center.
15 March 2019	The inclusion of patients with Achilles tendinopathy and addition of a new center.
18 September 2019	Addition of 1 new center and change of Principal Investigator from another center

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported