

**Clinical trial results:****ONCOFID-P (Paclitaxel-hyaluronic acid) in the intravesical therapy of patients with non-muscle invasive cancer of the bladder. A phase II marker lesion study****Summary**

EudraCT number	2009-012274-13
Trial protocol	IT ES DE
Global end of trial date	30 March 2017

Results information

Result version number	v1 (current)
This version publication date	09 August 2022
First version publication date	09 August 2022

Trial information**Trial identification**

Sponsor protocol code	R39-09-01
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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	Nicola Giordan, Fidia Farmaceutici, +39 0498232111, ngiordan@fidiapharma.it
Scientific contact	Nicola Giordan, Fidia Farmaceutici, +39 0498232111, ngiordan@fidiapharma.it
Sponsor organisation name	Linical
Sponsor organisation address	Calle Las Norias 92, Madrid, Spain,
Public contact	Carlos M. Hortelano, Linical, +34 91 372 60 00,
Scientific contact	Carlos M. Hortelano, Linical, +34 91 372 60 00,

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	27 September 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 October 2016
Global end of trial reached?	Yes
Global end of trial date	30 March 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess, at control visit (V8), the ablative activity of intravesical administration of Oncofid-P-B on a papillary marker tumor on patients suffering from multiple recurrent Ta G1-G2 papillary cancer of the bladder after 6 weeks of weekly study drug administration, through number and percentage of patients with Complete Response

Protection of trial subjects:

The proced documentation of the study were designed to ensure that both the Sponsor and the Investigator strictly adhere to the ethical principles laid down in the current revision of the Declaration of Helsinki. The study was also carried out according both to the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines and local legal and regulatory requirements. Before being admitted to the study, the patient was fully informed of its nature, score and possible implications. The study was explained in a written form understandable to him/her, and the form signed by him/her. For incapacitated adults and patients under emergency situation and incapable to give consent, the written consent of the legally authorised representative was provided.

Background therapy:

No other therapies were administered in the framework of the study.

Evidence for comparator: -

Actual start date of recruitment	17 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	Germany: 12
Country: Number of subjects enrolled	Italy: 15
Country: Number of subjects enrolled	Spain: 33
Worldwide total number of subjects	60
EEA total number of subjects	60

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)	60
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

- Patients of both sexes aged > 18 years
- Cytological or histological diagnosis of bladder cancer;
- Multiple primary or recurrent Ta G1-G2 papillary cancer;
- ECOG Performance Status 0 to 1;
- Adequate bone marrow function: neutrophils $\geq 1.5 \times 10^3/\text{mL}$; platelet count $\geq 100 \times 10^3/\text{mm}^3$; haemoglobin (hb) $\geq 10 \text{ g/dL}$
- Written informed consent;

Period 1

Period 1 title	Oncofid-P-B 6W
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Oncofid-P-B
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Arm description:

A first treatment phase with a duration of 6 weeks

Arm type	Experimental
Investigational medicinal product name	Oncofid-P-B
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for intravesical solution
Routes of administration	Intravesical use

Dosage and administration details:

The preparation of diluted solutions will be performed by the following steps:

- Take 40 mL of concentrate solution (see the table below);
- Pour the content in a 100 mL empty vial;
- Add 10 mL of glucosate solution;
- Mix the final solution;
- Administer the solution

Number of subjects in period 1	Oncofid-P-B
Started	60
Completed	60

Period 2

Period 2 title	Oncofid-P-B 6+6 months
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

A second treatment maintenance phase with a treatment duration of 6+6 months (comprehensively 52 weeks)

Arms

Arm title	Oncofid-P-B 6+6
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Oncofid-P-B
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for intravesical solution
Routes of administration	Intravesical use

Dosage and administration details:

The preparation of diluted solutions will be performed by the following steps:

- Take 40 mL of concentrate solution (see the table below);
- Pour the content in a 100 mL empty vial;
- Add 10 mL of glucosate solution;
- Mix the final solution;
- Administer the solution

Number of subjects in period 2^[1]	Oncofid-P-B 6+6
Started	24
Completed	24

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: 60 patients completed the initial treatment period but only the patients that had a complete response at the end of this period (n=24) entered the maintenance period,

Baseline characteristics

Reporting groups

Reporting group title	Oncofid-P-B 6W
Reporting group description: -	

Reporting group values	Oncofid-P-B 6W	Total	
Number of subjects	60	60	
Age categorical			
The mean age \pm standard deviation (SD) of patients was 65.3 \pm 10.5 years old ranging between 44 and 87 years old. The proportion of the male population was 80.0% (48 out of the 60 patients included) and the proportion of the female population was 20.0%, being all patients of Caucasian race			
Units: Subjects			
Adults (18-64 years)	60	60	
Gender categorical			
Units: Subjects			
Female	12	12	
Male	48	48	

Subject analysis sets

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

Subject analysis set description:

Safety and efficacy analyses for the initial treatment phase will be conducted on all patients receiving at least one dose of the study drug.

Subject analysis set title	Per Protocol
Subject analysis set type	Per protocol

Subject analysis set description:

The PP will consist of all patients that received at least any amount of study drug and completed V8 without a major protocol deviation.

Reporting group values	Safety Population	Per Protocol	
Number of subjects	60	52	
Age categorical			
The mean age \pm standard deviation (SD) of patients was 65.3 \pm 10.5 years old ranging between 44 and 87 years old. The proportion of the male population was 80.0% (48 out of the 60 patients included) and the proportion of the female population was 20.0%, being all patients of Caucasian race			
Units: Subjects			
Adults (18-64 years)	60	52	
Gender categorical			
Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	Oncofid-P-B
Reporting group description: A first treatment phase with a duration of 6 weeks	
Reporting group title	Oncofid-P-B 6+6
Reporting group description: -	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description: Safety and efficacy analyses for the initial treatment phase will be conducted on all patients receiving at least one dose of the study drug.	
Subject analysis set title	Per Protocol
Subject analysis set type	Per protocol
Subject analysis set description: The PP will consist of all patients that received at least any amount of study drug and completed V8 without a major protocol deviation.	

Primary: Response rate at Visit 8-Safety Population

End point title	Response rate at Visit 8-Safety Population ^[1]
End point description: Complete response was defined as complete disappearance of the marker lesion, as confirmed by negative post-treatment cystoscopy including a biopsy at the marker lesion site and the absence of new tumors at other site and negative cytology.	
End point type	Primary
End point timeframe: Estimated at Visit 8, after 6 weeks of weekly study drug administration.	
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 analyses for this end point	

End point values	Oncofid-P-B			
Subject group type	Reporting group			
Number of subjects analysed	60			
Units: percentage protection				
number (confidence interval 90%)				
Safety population	45 (34.0 to 56.4)			

Statistical analyses

No statistical analyses for this end point

Primary: Response rate at Visit 8- Per Protocol

End point title	Response rate at Visit 8- Per Protocol ^[2]
End point description: Complete response was defined as complete disappearance of the marker lesion, as confirmed by negative post-treatment cystoscopy including a biopsy at the marker lesion site and the absence of new	

tumors at other site and negative cytology.

End point type	Primary
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End point timeframe:

Estimated at Visit 8, after 6 weeks of weekly study drug administration.

Notes:

[2] - 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 analyses for this end point

End point values	Oncofid-P-B			
Subject group type	Reporting group			
Number of subjects analysed	52			
Units: percentage protection				
number (confidence interval 90%)	46.2 (34.2 to 58.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number and percentage of patients with relapse within V22-Safety Population

End point title	Number and percentage of patients with relapse within V22-Safety Population
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End point description:

Regards to patients with relapse, defined as those patients who had no response, during the maintenance,

End point type	Secondary
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End point timeframe:

Patients with relapse within Visit 22.

End point values	Oncofid-P-B 6+6			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: percentage protection				
median (confidence interval 90%)	50 (31.9 to 68.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to relapse after Oncofid-P-B instillation-Safety Population

End point title	Time to relapse after Oncofid-P-B instillation-Safety Population
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End point description:

Regards to patients with relapse, defined as those patients who had no response, during the maintenance.

End point type	Secondary
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End point timeframe:

During the maintenance period

End point values	Oncofid-P-B 6+6			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: percent				
median (full range (min-max))	15.07 (7.6 to 15.70)			

Statistical analyses

No statistical analyses for this end point

Secondary: Evaluate the safety profile of Oncofid-P-B-Safety Population

End point title	Evaluate the safety profile of Oncofid-P-B-Safety Population
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End point description:

The secondary objectives were to determine the safety profile of Oncofid-P-B after the first administration and to assess tumor response.

End point type	Secondary
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End point timeframe:

During the 6 weeks instillation

End point values	Oncofid-P-B			
Subject group type	Reporting group			
Number of subjects analysed	60			
Units: 1.1	27			

Statistical analyses

No statistical analyses for this end point

Secondary: Evaluate the safety profile of Oncofid-P-B-Per Protocol

End point title	Evaluate the safety profile of Oncofid-P-B-Per Protocol
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End point description:

The secondary objectives were to determine the safety profile of Oncofid-P-B after the first administration and to assess tumor response.

End point type	Secondary
End point timeframe:	
During the 6 weeks instillation	

End point values	Oncofid-P-B			
Subject group type	Reporting group			
Number of subjects analysed	52			
Units: 1.1	24			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

17 May 2010-04 November 2016

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17
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Reporting groups

Reporting group title	Oncofid-P-B
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Reporting group description: -

Serious adverse events	Oncofid-P-B		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 60 (16.67%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pneumonia			
subjects affected / exposed	2 / 60 (3.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Urinary tract infection			
subjects affected / exposed	2 / 60 (3.33%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		

Post procedural haematuria subjects affected / exposed	3 / 60 (5.00%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Renal failure subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematuria subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Oncofid-P-B		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 60 (48.33%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Hypotension			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	2 / 60 (3.33%)		
occurrences (all)	2		
Reproductive system and breast disorders			
Erectile dysfunction			

subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Respiratory, thoracic and mediastinal disorders Haemoptysis subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Psychiatric disorders Libido decreased subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all) Tachycardia subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1 1 / 60 (1.67%) 1		
Nervous system disorders Syncope subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1 1 / 60 (1.67%) 1 2 / 60 (3.33%) 2		
Hepatobiliary disorders			

Hyperbilirubinaemia subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Hypertransaminasaemia subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Renal and urinary disorders Bladder discomfort subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Bladder spasm subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Dysuria subjects affected / exposed occurrences (all)	2 / 60 (3.33%) 2		
Haematuria subjects affected / exposed occurrences (all)	7 / 60 (11.67%) 3		
Micturition urgency subjects affected / exposed occurrences (all)	2 / 60 (3.33%) 2		
Reduced bladder capacity subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Urine abnormality subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Urine flow decreased subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Musculoskeletal and connective tissue disorders			

Back pain subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Infections and infestations Genital infection fungal subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Herpes zoster subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Urinary tract infection subjects affected / exposed occurrences (all)	14 / 60 (23.33%) 12		
Metabolism and nutrition disorders Hyperglycaemia subjects affected / exposed occurrences (all)	8 / 60 (13.33%) 5		
Hyperuricaemia subjects affected / exposed occurrences (all)	2 / 60 (3.33%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 July 2012	<p>The decision to amend the protocol was made in light of the difficulties in identifying sufficient numbers of eligible participants, and in response to the growing need to effectively improve the patient recruitment.</p> <p>The main changes to the protocol concern the inclusion/exclusion criteria. In particular, the study population was enlarged by the addition of patients with multiple primary Ta G1-G2 papillary cancer.</p> <p>Additionally, it was decided to allow the participation of subjects:</p> <ul style="list-style-type: none">- with a history of malignancies other than cancer of the upper urinary tract, cancer of the prostatic urethra and carcinoma in situ diagnosed more than 3 years before enrollment,- with cardiovascular diseases that are not considered to be a contraindication for intravesical treatment. <p>We would underline that the above mentioned changes in the patient population will not in any way affect patients safety and security, and will not impact the study results or the risk/benefit ratio of the study, and that they were done in respect to the guidelines of the European Organization for Research and Treatment of Cancer (EORTC) and the Medical Research Council for lesion marker trials.</p> <p>Other changes proposed in the present amendment are minor corrections of the protocol and the protocol synopsis, and the clarification with regard to some items as deemed necessary during the conduct of the study.</p> <p>We attach herewith the detailed summary of changes for more information ("Comparative table protocol final version 02/version 03", Version 1.0 dated 16 July 2012).</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported