Clinical trial results:
An open label, multiple dose, Phase III clinical study in patients with prostate cancer to investigate the clinical efficacy of AMW goserelin 3.6 mg implant in its application system

Summary

EudraCT number	2014-002484-15
Trial protocol	DE
Global end of trial date	25 May 2016

Results information

Result version number	v1 (current)
This version publication date	10 September 2021
First version publication date	10 September 2021

Trial information

Trial identification

Sponsor protocol code	AMW/004/C

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AMW GmbH
Sponsor organisation address	Birkerfeld 11, Warngau, Germany, 83627
Public contact	Chief Executive Officer, AMW GmbH, +49 80244709990, info@a-m-w.eu
Scientific contact	Kerstin Hofmann, Head Clinical Research Department, AMW GmbH, +49 80244709990, k.hofmann@a-m-w.eu

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	18 August 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 May 2016
Global end of trial reached?	Yes
Global end of trial date	25 May 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

• To investigate the efficacy of goserelin 3.6 mg implant (when applied every 28 days for 56 days) in suppression of testosterone levels below castrate level (0.5 ng/ml). The study will be considered a successful bridging study, if the response rate, i.e., the percentage of patients with plasma testosterone levels below castrate level (0.5 ng/ml) on Days 28 and 56 (at Visits 4 and 6), will be at least 90% in the patients of the modified full analysis set (see Primary efficacy endpoint).
• To demonstrate correct functionality of the application system, as assessed by an increase of plasma goserelin levels to a value above the Lower Limit of Quantification (LLOQ) (i.e., presence of goserelin in plasma) and as assessed by the investigator with confirmation by a witness.

Protection of trial subjects:

close monitoring of all subjects during the study including safety monitoring:
• Findings from digital rectal examination of the prostate,
• Adverse Events (AEs),
• Vital signs (blood pressure, heart rate), body weight and temperature,
• Safety laboratory parameters
• local tolerability of the implant

Background therapy: -

Evidence for comparator:

This is a single arm, non-comparative study.

Actual start date of recruitment	13 January 2016
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: 33
Worldwide total number of subjects	33
EEA total number of subjects	33

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)	4
From 65 to 84 years	26
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Overall, 36 patients were screened for the study. Three patients were screening failures. 33 patients were considered eligible at baseline and received study medication. Two clinical sites in Germany were involved in recruitment.

Pre-assignment

Screening details:

Screening procedures were performed up to 2 weeks prior application of the first implant:
- Informed Consent
- Demography, Medical history, concomitant diseases
- Concomitant medications
- Inclusion/ Exclusion criteria
- full physical examination
- Body weight, sublingual temperature
- Vital signs
- Safety lab
- Testosteron determination

Period 1

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

Blinding implementation details:

uncontrolled, open label

Arms

Arm title	Application Goserelin 3.6 mg implant

Arm description:

Two subcutaneous applications of AMW Goserelin 3.6 mg implant, on Day 0 and on Day 28 (total duration of treatment 56 days)

Arm type	Experimental
Investigational medicinal product name	AMW Goserelin 3.6 mg Implantat
Investigational medicinal product code	C0005AMW0802IMP
Other name	
Pharmaceutical forms	Implant
Routes of administration	Subcutaneous use

Dosage and administration details:

Goserelin 3.6 mg implant was injected by a physician subcutaneously into the anterior abdominal wall at Day 0 and Day 28 according to the application instruction provided. Assessments concerning the applicator and its (correct) functionality was be made, a witness observed and also assessed the preparation for injection and the actual injection.
In case the applicator failed the initial visual inspection or showed signs of non- functioning during preparation, injection or after injection, another applicator had to be used if necessary to achieve a successful implantation. Details had to be documented in the CRF and had to be reported to the CRO and the sponsor immediately. Any defective applicator had be sent to the sponsor for inspection as soon as possible. The duration of treatment in this study was two months (56 days) with two applications of goserelin.

Number of subjects in period 1	Application Goserelin 3.6 mg implant
Started	33
Completed	33

Baseline characteristics

Reporting groups

Reporting group title	overall trial

Reporting group description:

all patients who received two subcutaneous applications of AMW Goserelin 3.6mg implant on day 0 and day 28 (total duration 56 days).

Reporting group values	overall trial	Total	
Number of subjects	33	33	
Age categorical			
- Males aged 18 years or older; - Histologically confirmed diagnosis of carcinoma of the prostate suitable for hormonal manipulation including patients; - with rising prostate-specific antigen (PSA) after having undergone surgery or radiotherapy with curative intention, - Normal testosterone value (> 10.4 nmol/L or > 3 ng/mL) at screening, according to immunoassay, - Life expectancy of at least six months, - The patient was capable of giving informed - The patient has given written informed consent			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	4	4	
From 65-84 years	26	26	
85 years and over	3	3	
Gender categorical			
Males aged 18 or older			
Units: Subjects			
Female	0	0	
Male	33	33	

Subject analysis sets

Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

33 patients were considered eligible at baseline and received study medication. These 33 patients were analysed i in the full analysis set (FAS). Additionally, a subset of the full analysis set (modified full analysis set, MFAS) was analysed, comprising all FAS patients for whom two injection times were documented in the case report form (CRF) and who did not terminate the study prematurely for reasons not causally related to lack of efficacy or safety of study medication. All 33 patients of the FAS were also included in the MFAS.

Subject analysis set title	Per Protocol (PP)
Subject analysis set type	Per protocol

Subject analysis set description:

The PP analysis set comprised 29 patients treated with study medication and without major protocol violations.

Reporting group values	Full Analysis Set (FAS)	Per Protocol (PP)	
Number of subjects	33	29	
Age categorical			
- Males aged 18 years or older; - Histologically confirmed diagnosis of carcinoma of the prostate suitable for hormonal manipulation including patients; - with rising prostate-specific antigen (PSA) after having undergone surgery or radiotherapy with curative intention, - Normal testosterone value (> 10.4 nmol/L or > 3 ng/mL) at screening, according to immunoassay, - Life expectancy of at least six months, - The patient was capable of giving informed - The patient has given written informed consent			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)	4	4	
From 65-84 years	26	22	
85 years and over	3	3	
Gender categorical			
Males aged 18 or older			
Units: Subjects			
Female	0	0	
Male	33	29	

End points

End points reporting groups

Reporting group title	Application Goserelin 3.6 mg implant

Reporting group description:

Two subcutaneous applications of AMW Goserelin 3.6 mg implant, on Day 0 and on Day 28 (total duration of treatment 56 days)

Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

33 patients were considered eligible at baseline and received study medication. These 33 patients were analysed i in the full analysis set (FAS). Additionally, a subset of the full analysis set (modified full analysis set, MFAS) was analysed, comprising all FAS patients for whom two injection times were documented in the case report form (CRF) and who did not terminate the study prematurely for reasons not causally related to lack of efficacy or safety of study medication. All 33 patients of the FAS were also included in the MFAS.

Subject analysis set title	Per Protocol (PP)
Subject analysis set type	Per protocol

Subject analysis set description:

The PP analysis set comprised 29 patients treated with study medication and without major protocol violations.

Primary: Percentage of patients with plasma testosterone below castrate level (0.5 ng/mL) at Visit 4 (Day 28) and visit 6 (day 56)

End point title	Percentage of patients with plasma testosterone below castrate level (0.5 ng/mL) at Visit 4 (Day 28) and visit 6 (day 56)[1]

End point description:

A patient was considered a responder (response = 'yes'), if both relevant values were below castrate level. If at least one of the two relevant values was equal to or above castrate level (i.e., ≥ 0.5 ng/mL), the patient was considered a non-responder (response = 'no'). If at least one of the two relevant values was missing, the patient was also considered a non-responder (response = 'no', conservative approach).

End point type	Primary

End point timeframe:

visit 4 (day 28) and visit 6 (day 56)

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: The primary endpoint was the percentage of patients with plasma testosterone below castrate level (0.5 ng/mL) at Visit 4 (Day 28) and visit 6 (day 56). In the FAS the percentage of patients with testosterone below castrate level at Visit 4 (Day 28) and Visit 6 (Day 56) (= response rate) was 93.94% with the corresponding exact 95% CI (79.77%; 99.26%). As the response rate was ≥90%, the study is considered a successful bridging study.

End point values	Application Goserelin 3.6 mg implant	Full Analysis Set (FAS)	Per Protocol (PP)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	33	33	29	
Units: 33	33	31	27	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients with an increase in plasma goserelin levels at Visit 3 (Day 14) and Visit 5 (Day 42) to a value above LLOQ

End point title	Percentage of patients with an increase in plasma goserelin levels at Visit 3 (Day 14) and Visit 5 (Day 42) to a value above LLOQ

End point description:

Goserelin plasma levels are summarised by visit and are listed by patient. The arithmetic mean including standard deviation and the median of goserelin plasma levels measured by LC- MS/MS at Visits 3 to 6for the FAS and PP set. From Visit 3 (Day 14) on, all mean and median values of goserelin plasma levels were above the LLOQ (0.200 ng/mL) in the FAS and in the PP set. The highest arithmetic mean and median values of goserelin plasma levels were detected at Visit 3 (Day 14) and Visit 5 (Day 42) in both analysis sets. At the end of the first and and second treatment cycle, i.e. at Visit 4 (Day 28) and Visit 6 (Day 56), arithmetic mean values and median values were still above the LLOQ of 0.200 ng/mL.

End point type	Secondary

End point timeframe:

visit 3 (day 14) and visit 5 (day 42)

End point values	Application Goserelin 3.6 mg implant	Full Analysis Set (FAS)	Per Protocol (PP)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	33	33	29	
Units: 33	33	28	24	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of applications with correct functionality of the application system

End point title	Percentage of applications with correct functionality of the application system

End point description:

Correct functionality of the application system of the implant at baseline (Day 0) and Visit 4 (Day 28) and percentage of applications with correct functionality of the application system. Data for correct functionality of the application system plus assessment by investigator and assessment by witness and initial visual inspection of the applicator.

End point type	Secondary

End point timeframe:

Visit 2 (study day 0, application implant) and visit 4 (day 28)

End point values	Application Goserelin 3.6 mg implant	Full Analysis Set (FAS)	Per Protocol (PP)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	33	33	29	
Units: 33	33	32	28	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients with an increase in plasma goserelin at Visit 3 (Day 14) to a value above LLOQ

End point title	Percentage of patients with an increase in plasma goserelin at Visit 3 (Day 14) to a value above LLOQ

End point description:

The percentage of patients with an increase in plasma goserelin levels at Visit 3 (Day 14) to a value above LLOQ. A patient was considered to fulfil this criterion, if the goserelin value was above LLOQ at Visit 3 (Day 14) and higher than the goserelin value at the previous visit, i.e. Visit 2 (Day 0). Goserelin was assumed to be <LLOQ at Visit 2 (Day 0). Therefore, a value >LLOQ at Visit 3 (Day 14) reflects an increase compared to the previous visit.

End point type	Secondary

End point timeframe:

visit 3 (day 14)

End point values	Application Goserelin 3.6 mg implant	Full Analysis Set (FAS)	Per Protocol (PP)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	33	33	29	
Units: 33	33	31	27	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients with an increase in plasma goserelin at Visit 5 (Day 42) to a value above LLOQ (i.e., presence of goserelin in plasma)

End point title	Percentage of patients with an increase in plasma goserelin at Visit 5 (Day 42) to a value above LLOQ (i.e., presence of goserelin in plasma)

End point description:

The percentage of patients with an increase in plasma goserelin levels at Visit 5 (Day 42) to a value above LLOQ (0.200 ng/mL). A patient was considered to fulfil this criterion, if the goserelin value was above LLOQ at Visit 5 (Day 42) and higher than the goserelin value at the previous visit, i.e. Visit 4 (Day 28).

End point type	Secondary

End point timeframe:

visit 5 (day 42)

End point values	Application Goserelin 3.6 mg implant	Full Analysis Set (FAS)	Per Protocol (PP)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	33	33	29	
Units: 33	33	28	24	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients with plasma testosterone below castrate level (0.5 ng/mL) at Visit 4 (Day 28)

End point title	Percentage of patients with plasma testosterone below castrate level (0.5 ng/mL) at Visit 4 (Day 28)

End point description:

The percentage of patients with plasma testosterone levels below castrate level (0.5 ng/mL) at Visit 4 (Day 28)

End point type	Secondary

End point timeframe:

visit 4 (day 28)

End point values	Application Goserelin 3.6 mg implant	Full Analysis Set (FAS)	Per Protocol (PP)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	33	33	29	
Units: 33	33	31	27	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients with plasma testosterone below castrate level (0.5 ng/mL) at Visit 6 (Day 56)

End point title	Percentage of patients with plasma testosterone below castrate level (0.5 ng/mL) at Visit 6 (Day 56)

End point description:

The percentage of patients with plasma testosterone levels below castrate level (0.5 ng/mL) at Visit 6 (Day 56).

End point type	Secondary

End point timeframe:

visit 6 (day 56)

End point values	Application Goserelin 3.6 mg implant	Full Analysis Set (FAS)	Per Protocol (PP)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	33	33	29	
Units: 33	33	31	27	

Statistical analyses

No statistical analyses for this end point

Secondary: Testosterone levels at baseline at Visit 2 (Day 0), Visit 4 (Day 28) and at Visit 6 (Day 56)

End point title	Testosterone levels at baseline at Visit 2 (Day 0), Visit 4 (Day 28) and at Visit 6 (Day 56)

End point description:

Testosterone plasma levels are summarised by visit and are listed by patient. The arithmetic mean including standard deviation and the median of testosterone plasma levels measured by LC- MS/MS at baseline Visit 2 (Day 0), Visit 4 (Day 28), and Visit 6 (Day 56) are reported for the FAS and PP set.

End point type	Secondary

End point timeframe:

Visit 2 (day 0), visit 4 (day 28) and visit 6 (56)

End point values	Application Goserelin 3.6 mg implant	Full Analysis Set (FAS)	Per Protocol (PP)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	33	33	29	
Units: 99				
number (not applicable)	33	33	29	

Statistical analyses

No statistical analyses for this end point

Secondary: Goserelin plasma levels at Visit 3 (Day 14) and Visit 5 (Day 42)

End point title	Goserelin plasma levels at Visit 3 (Day 14) and Visit 5 (Day 42)

End point description:

Goserelin plasma levels are summarised by visit and are listed by patient The arithmetic mean including standard deviation and the median of goserelin plasma levels measured by LC- MS/MS at Visits 3 (Day 14) and 5 (Day 42) are summarised for the FAS and PP set.

End point type	Secondary

End point timeframe:
visit 3 (day 14) and visit 5 (day 42)

End point values	Application Goserelin 3.6 mg implant	Full Analysis Set (FAS)	Per Protocol (PP)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	33	33	29	
Units: 66				
number (not applicable)	33	33	29	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Visit 2 (study day 0, application of implant) to visit 6 (study day 56)

Adverse event reporting additional description:

AEs were coded using MedDRA and were summarized by SOC and PT. All AEs were listed in by patient listings. The following categories were analysed using summary tables presenting absolute and relative frequencies: treatment-emergent AEs, SAEs, deaths, causally related AEs and AEs leading to discontinuation.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	study safety analysis set

Reporting group description:

group includes all patients with applied implants

Serious adverse events	study safety analysis set		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 33 (3.03%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Musculoskeletal and connective tissue disorders			
Metastases to bone	Additional description: mild severity, unrelated causality, treatment emergent, no premature termination of patient.		
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1000		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	study safety analysis set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 33 (33.33%)		
Investigations			
Gamma-glutamyltransferase increased			

subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Vascular disorders Flushing subjects affected / exposed occurrences (all) Hot flush subjects affected / exposed occurrences (all) Hypertension subjects affected / exposed occurrences (all)	 2 / 33 (6.06%) 2 5 / 33 (15.15%) 5 1 / 33 (3.03%) 1		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Feeling cold subjects affected / exposed occurrences (all)	 1 / 33 (3.03%) 1 1 / 33 (3.03%) 1		
Reproductive system and breast disorders Testicular atrophy subjects affected / exposed occurrences (all)	 1 / 33 (3.03%) 1		
Psychiatric disorders Sleep disorder subjects affected / exposed occurrences (all)	 1 / 33 (3.03%) 1		
Musculoskeletal and connective tissue disorders Bone pain subjects affected / exposed occurrences (all) Muscle atrophy subjects affected / exposed occurrences (all)	 1 / 33 (3.03%) 1 1 / 33 (3.03%) 1		
Infections and infestations			

Bronchitis bacterial subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	 1 / 33 (3.03%) 1 2 / 33 (6.06%) 2 1 / 33 (3.03%) 1		
Metabolism and nutrition disorders Increased appetite subjects affected / exposed occurrences (all)	 1 / 33 (3.03%) 1		

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