Clinical trial results:
Phase II, single centre, double blinded, cross-over dose confirmation study using two morphine-naloxone i.v. solutions

Summary

EudraCT number	2011-005903-34
Trial protocol	AT
Global end of trial date	02 August 2016

Results information

Result version number	v1 (current)
This version publication date	18 April 2022
First version publication date	18 April 2022

Trial information

Trial identification

Sponsor protocol code	KKSMUW2011-09

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	G.L. Pharma GmbH
Sponsor organisation address	Schlossplatz 1, Lannach, Austria, 8502
Public contact	G. L. Pharma GmbH, G. L. Pharma GmbH, +43 3136825770, office@gl-pharma.at
Scientific contact	G. L. Pharma GmbH, G. L. Pharma GmbH, +43 3136825770, office@gl-pharma.at

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	16 January 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 January 2016
Global end of trial reached?	Yes
Global end of trial date	02 August 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the appropriate ratio of morphine and naloxone to suppress the pleasurable effects of intravenous morphine and precipitate withdrawal reactions.

Protection of trial subjects:

health monitoring personnel, rescue medication, measurements of vital signs

Background therapy:

diagnosis of opioid dependence currently undergoing morphine maintenance treatment

Evidence for comparator: -

Actual start date of recruitment	09 January 2013
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	Austria: 56
Worldwide total number of subjects	56
EEA total number of subjects	56

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)	56
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

2013 - 2015, Austria

Pre-assignment

Screening details:

vital signs, complete blood count, medical history, inclusion/exclusion criteria,

Pre-assignment period milestones

Number of subjects started	56
Intermediate milestone: Number of subjects	oral morphine: 44
Number of subjects completed	44

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screening failure: 10
Reason: Number of subjects	Consent withdrawn by subject: 2

Period 1

Period 1 title	Morphine i.v.
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Morphine i.v.

Arm description: -

Arm type	Baseline
Investigational medicinal product name	Morphine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

individual doses

Number of subjects in period 1[1]	Morphine i.v.
Started	44
Completed	43
Not completed	1
Consent withdrawn by subject	1

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: A number of 56 subjects were enrolled for screening. There were 10 screening failures, and 2 subjects withdraw their consent. Finally, 44 subjects started the baseline period.

Period 2

Period 2 title	Morphine-Naloxone 100:1 vs. Morphine
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Data analyst, Carer, Assessor, Subject

Arms

Are arms mutually exclusive?	No
Arm title	Morphine-Naloxone ratio 100:1 i.v.

Arm description: -

Arm type	Experimental
Investigational medicinal product name	MorphineNaloxone 100:1 Ampoules / Solution for Injection
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

individual doses

Arm title	Morphine Mono1

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Morphine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

individual doses

Number of subjects in period 2	Morphine-Naloxone ratio 100:1 i.v.	Morphine Mono1
Started	43	43
Completed	43	42
Not completed	0	1
Consent withdrawn by subject	-	1

Period 3	
Period 3 title	Morphine-Naloxone 200:1 vs. Morphine
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms	
Are arms mutually exclusive?	No
Arm title	Morphine-Naloxone ratio 200:1 i.v.
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	MorphineNaloxone 200:1 Ampoules / Solution for Injection
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use
Dosage and administration details: individual doses	
Arm title	Morphine Mono2
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Morphine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use
Dosage and administration details: individual doses	

Number of subjects in period 3	Morphine-Naloxone ratio 200:1 i.v.	Morphine Mono2
Started	42	42
Completed	40	42
Not completed	2	0
Adverse event, non-fatal	1	-
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Morphine i.v.

Reporting group description: -

Reporting group values	Morphine i.v.	Total	
Number of subjects	44	44	
Age categorical			
all subjects			
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)	0	0	
From 65-84 years	44	44	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	0	0	
Male	44	44	

End points

End points reporting groups

Reporting group title	Morphine i.v.
Reporting group description: -	
Reporting group title	Morphine-Naloxone ratio 100:1 i.v.
Reporting group description: -	
Reporting group title	Morphine Mono1
Reporting group description: -	
Reporting group title	Morphine-Naloxone ratio 200:1 i.v.
Reporting group description: -	
Reporting group title	Morphine Mono2
Reporting group description: -	

Primary: AUC(0-20) of SOWS-G

End point title	AUC(0-20) of SOWS-G[1]

End point description:

Signs and symptoms of opiatewithdrawal, according to Short Opiate Withdrawal Scale German (SOWSG), AUC of Total Score between 0 and 20 minutes after application of study drug.

End point type	Primary

End point timeframe:

0 and 20 minutes after application of study drug

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 study was carried out in a cross-over design. No statistical analysis was reported to prevent automated summing up of the arms population.
For the primary endpoint SOWS-G , 42 subjects were included. The analysis was pre-specified, the analysis type was superiority with a p-value of
< 0.05. The method used was Wilcoxon (Mann-Whitney).

End point values	Morphine-Naloxone ratio 100:1 i.v.	Morphine-Naloxone ratio 200:1 i.v.	Morphine Mono1	Morphine Mono2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	40	42	40
Units: total score * minutes				
geometric mean (standard deviation)	239 (± 127)	104 (± 110)	21 (± 37)	18 (± 36)

Statistical analyses

No statistical analyses for this end point

Primary: AUC of Pupil diameter

End point title	AUC of Pupil diameter[2]

End point description:

Pupil diameter, mean of left and right eye, AUC between 0 and 20 minutes after application of study drug.

End point type	Primary

End point timeframe:

0-20 minutes after administration of study drug

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: The study was carried out in a cross-over design. No statistical analysis was reported to prevent automated summing up of the arms population.
For the primary endpoint pupil diameter, 42 subjects were included. The analysis was pre-specified, the analysis type was superiority with a p-value of
< 0.05. The method used was Wilcoxon (Mann-Whitney).

End point values	Morphine-Naloxone ratio 100:1 i.v.	Morphine-Naloxone ratio 200:1 i.v.	Morphine Mono1	Morphine Mono2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	41	40	41	40
Units: mm * minutes				
geometric mean (standard deviation)	17.1 (± 10.5)	13.7 (± 11.2)	-10.2 (± 8.2)	-10.6 (± 10.3)

Statistical analyses

No statistical analyses for this end point

Secondary: AUC(0-20) of OOWS

End point title	AUC(0-20) of OOWS
End point description:	
Objective Opiate Withdrawal Scale	
End point type	Secondary
End point timeframe:	
0-20 minutes	

End point values	Morphine-Naloxone ratio 100:1 i.v.	Morphine-Naloxone ratio 200:1 i.v.	Morphine Mono1	Morphine Mono2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	40	42	40
Units: total score * minutes				
geometric mean (standard deviation)	131 (± 43)	68 (± 42)	7 (± 11)	5 (± 9)

Statistical analyses

No statistical analyses for this end point

Secondary: AUC(0-20) of Wang scale

End point title	AUC(0-20) of Wang scale
End point description:	
Wang Scale (third)	

End point type	Secondary

End point timeframe:

0-20 minutes

End point values	Morphine-Naloxone ratio 100:1 i.v.	Morphine-Naloxone ratio 200:1 i.v.	Morphine Mono1	Morphine Mono2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	21	23	21
Units: total score * minutes				
geometric mean (standard deviation)	253 (± 148)	67 (± 77)	2 (± 7)	1 (± 2)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: full report	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	10
Reporting groups	
Reporting group title	all subjects

Reporting group description: -

Serious adverse events	all subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 44 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	all subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 44 (47.73%)		
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences (all)	2		
Dysgeusia			

subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Coma			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Injection site erythema			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Injection site urticaria			
subjects affected / exposed	5 / 44 (11.36%)		
occurrences (all)	7		
Injection site plaque			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences (all)	2		
Flatulence			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	3		
Abdominal pain upper			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences (all)	2		
Enteritis			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences (all)	2		
Diarrhoea			

subjects affected / exposed	8 / 44 (18.18%)		
occurrences (all)	9		
Vomiting			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences (all)	3		
Urticaria			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Psychiatric disorders			
Sleep disorder			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Infections and infestations			
Abscess limb			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 July 2012	Change of principal investigator
30 August 2013	Addition of an additional questionnaire for the subjects
15 April 2014	Adjustments to safety reporting and informed consent
17 October 2014	Change of principal investigator

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported