



## Clinical trial results:

### Open label clinical study to evaluate the safety and efficacy of ProvayBlue™ (methylene blue injection USP) for the treatment of acquired methemoglobinemia

#### Summary

EudraCT number	2017-000290-37
Trial protocol	FR GB
Global end of trial date	09 December 2021

#### Results information

Result version number	v1 (current)
This version publication date	21 July 2022
First version publication date	21 July 2022

#### Trial information

##### Trial identification

Sponsor protocol code	PVP-2016003
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03395223
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Provepharm SAS
Sponsor organisation address	22 rue Marc Donadille, Marseille, France, 13013
Public contact	Clinical Trials Information, Provepharm SAS, +33 491086930,
Scientific contact	Clinical Trials Information, Provepharm SAS, +33 491086930,

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	09 December 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 December 2021
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The primary objective was to confirm that ProvayBlue is efficacious in patients with acquired methemoglobinemia.

Protection of trial subjects:

NA

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 October 2017
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	France: 6
Country: Number of subjects enrolled	United States: 25
Worldwide total number of subjects	31
EEA total number of subjects	6

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)	29
From 65 to 84 years	2
85 years and over	0

## Subject disposition

### Recruitment

#### Recruitment details:

Pediatric or adult patients (males and females of all ages) diagnosed with acquired methemoglobinemia and receiving treatment with ProvayBlue per the treating physician's diagnosis and hospital/urgent care/acute care facility's standard care.

Acquired methemoglobinemia was defined as a level of methHb >30% or ≤30% with associated clinical symptoms.

### Pre-assignment

#### Screening details:

Subjects who presented in a hospital/urgent care setting with acquired methemoglobinemia, defined as a methHb level of 30% or higher and/or symptoms referable to reduced oxygen-carrying capacity and resulting respiratory distress, alteration in mental status, sleepiness, cyanosis, dizziness, etc.

### Pre-assignment period milestones

Number of subjects started	31
Number of subjects completed	31

### Period 1

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

### Arms

Arm title	Overall Period
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#### Arm description:

Pediatric or adult patients (males and females of all ages) diagnosed with acquired methemoglobinemia and receiving treatment with ProvayBlue per the treating physician's diagnosis and hospital/urgent care/acute care facility's standard care.

Acquired methemoglobinemia was defined as a level of methHb >30% or ≤30% with associated clinical symptoms.

Arm type	Experimental
Investigational medicinal product name	ProvayBlue (Methylthioninium Chloride Proveblue)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

#### Dosage and administration details:

Subjects were administered ProvayBlue IV over 5 to 30 minutes, usually at a dose of 1 mg/kg, and, if the methHb level remained above 30% or clinical symptoms persisted, a repeat dose of up to 1 mg/kg was to be administered 1 hour after the first dose

<b>Number of subjects in period 1</b>	Overall Period
Started	31
Completed	31

## Baseline characteristics

### Reporting groups

Reporting group title	Overall period
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Reporting group description: -

Reporting group values	Overall period	Total	
Number of subjects	31	31	
Age categorical			
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)	29	29	
From 65-84 years	2	2	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female	18	18	
Male	13	13	

## End points

### End points reporting groups

Reporting group title	Overall Period
Reporting group description: Pediatric or adult patients (males and females of all ages) diagnosed with acquired methemoglobinemia and receiving treatment with ProvayBlue per the treating physician's diagnosis and hospital/urgent care/acute care facility's standard care. Acquired methemoglobinemia was defined as a level of methHb >30% or ≤30% with associated clinical symptoms.	

### Primary: Efficacy endpoints: changes from baseline in methHb levels

End point title	Efficacy endpoints: changes from baseline in methHb levels <sup>[1]</sup>
End point description: The primary efficacy endpoint was the number (%) of subjects with ≥50% reduction in methHb based on the first available posttreatment assessment when the first posttreatment measurement was taken within 2 hours of completion of first infusion.	
End point type	Primary
End point timeframe: Before and after ProvayBlue infusion	

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 results are presented as a series of individual patient narratives with limited statistical analysis, befitting the observational nature of most of the data. Test

Hypothesis and P Value Justification is not applicable since no inferential statistics are provided for this study.

End point values	Overall Period			
Subject group type	Reporting group			
Number of subjects analysed	9 <sup>[2]</sup>			
Units: Number of subjects with 50% reduction	8			

Notes:

[2] - 9 subjects had MethHb level assessed within 2 hours of the end of the first ProvayBlue treatment

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Prevalence and nature of TEAEs, defined as all adverse events (AEs) with an onset date after the first dose of ProvayBlue infusion and within 10 days of the last dose of ProvayBlue infusion

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	23
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### Reporting groups

Reporting group title	Safety analysis set
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Reporting group description:

All 31 enrolled subjects received at least 1 ProvayBlue infusion and were included in the Safety Analysis Set.

Serious adverse events	Safety analysis set		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 31 (9.68%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Vascular disorders			
Thrombosis			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Seizure-like phenomena			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Methemoglobinemia			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

<b>Non-serious adverse events</b>	Safety analysis set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 31 (25.81%)		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Myoclonus			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
Gastrointestinal disorders			
diarrhea			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hypokalemia			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Hypomagnesaemia			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
31 August 2020	A total of 31 subjects were enrolled into the study. The study was early closed owing to the rarity of the clinical presentation of interest.	-

Notes:

### Limitations and caveats

None reported