Clinical trial results:
THE USE OF ADV6209 FOR PREMEDICATION IN PAEDIATRIC ANAESTHESIA: A CONTROLLED, RANDOMIZED, DOUBLE BLINDED STUDY

Summary

EudraCT number	2019-001853-25
Trial protocol	AT
Global end of trial date	17 September 2021

Results information

Result version number	v1 (current)
This version publication date	20 October 2022
First version publication date	20 October 2022
Summary attachment (see zip file)	Publication_ADV6209 (pharmaceutics-ADV6209.pdf)

Trial information

Trial identification

Sponsor protocol code	1.2-24.05.2019

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03931057
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medical University Vienna
Sponsor organisation address	Spitalgasse 23, Vienna, Austria, 1090
Public contact	Dept. of Paediatric Anaesthesia, Medical University of Vienna, 0043 14040019227, peter.marhofer@meduniwien.ac.at
Scientific contact	Dept. of Paediatric Anaesthesia, Medical University of Vienna, 0043 14040019227, peter.marhofer@meduniwien.ac.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	17 September 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 September 2021
Global end of trial reached?	Yes
Global end of trial date	17 September 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of ADV6209, a new oral Midazolam formulation, on preoperative anxiety and sedation levels in paediatric anaesthesia

Primary Objective: Sedation score (mYPAS) 30 min after administration of the premedication drug

Protection of trial subjects:

All participants got premedication to minimize stress

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 November 2020
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: 80
Worldwide total number of subjects	80
EEA total number of subjects	80

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)	80
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The participants were recruited at the department of pediatric anaesthesia / surgery of the Medical University Vienna

Pre-assignment

Screening details:

90 participants were screened - 80 were enrolled, 10 were excluded because the parents / legal guardians denied the participation

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	ADV6209

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Ozalin
Investigational medicinal product code	ADV6209
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

one single oral dose of 0.25 mg/kg

Arm title	Dormicum

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Dormicum
Investigational medicinal product code	
Other name	Midazolam
Pharmaceutical forms	Solution for injection
Routes of administration	Oral use

Dosage and administration details:

one single dose of 0.25 mg/kg

Number of subjects in period 1	ADV6209	Dormicum
Started	40	40
Completed	40	40

Baseline characteristics

Reporting groups	
Reporting group title	ADV6209
Reporting group description: -	
Reporting group title	Dormicum
Reporting group description: -	

Reporting group values	ADV6209	Dormicum	Total
Number of subjects	40	40	80
Age categorical			
Children aged 2-8 years were included			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	40	40	80
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical			
male and female subjects were included			
Units: Subjects			
Female	12	13	25
Male	28	27	55

Subject analysis sets	
Subject analysis set title	all subjects
Subject analysis set type	Full analysis

Subject analysis set description:

A Kolmogorov–Smirnov test was used to check for normal distribution, followed by a non-parametric Mann–Whitney U-test for intergroup comparisons of metric and not normally distributed data, namely mYPAS-SF scores at baseline (i.e., before premedication) and 30 min later (i.e., immediately before mask induction). Absolute differences between both of these points in time was further categorized as (1) unchanged scores indicating no effect, (2) higher scores indicating an unfavorable effect and (3) lower scores indicating a favorable effect on anxiety. For intergroup comparisons of proportions, we used cross-tabulation and the Pearson’s chi-square test. The chances of false-positive results (type I errors) from multiple testing were reduced by Bonferroni correction, results expressed as medians with interquartile ranges (IQRs) and/or absolute values with percentages and differences considered significant atp< 0.05. All operations were performed with IBM®

Reporting group values	all subjects		
Number of subjects	80		
Age categorical			
Children aged 2-8 years were included			
Units: Subjects			

In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
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Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Gender categorical			
male and female subjects were included			
Units: Subjects			
Female	25		
Male	55		

End points

End points reporting groups

Reporting group title	ADV6209
Reporting group description: -	
Reporting group title	Dormicum
Reporting group description: -	
Subject analysis set title	all subjects
Subject analysis set type	Full analysis

Subject analysis set description:

A Kolmogorov–Smirnov test was used to check for normal distribution, followed by a non-parametric Mann–Whitney U-test for intergroup comparisons of metric and not normally distributed data, namely mYPAS-SF scores at baseline (i.e., before premedication) and 30 min later (i.e., immediately before mask induction). Absolute differences between both of these points in time was further categorized as (1) unchanged scores indicating no effect, (2) higher scores indicating an unfavorable effect and (3) lower scores indicating a favorable effect on anxiety. For intergroup comparisons of proportions, we used cross-tabulation and the Pearson’s chi-square test. The chances of false-positive results (type I errors) from multiple testing were reduced by Bonferroni correction, results expressed as medians with interquartile ranges (IQRs) and/or absolute values with percentages and differences considered significant atp< 0.05. All operations were performed with IBM®

Primary: Patient anxiety 30 min after the premedication

End point title	Patient anxiety 30 min after the premedication

End point description:

End point type	Primary

End point timeframe:

The primary endpoint of the study was patient anxiety 30 min after administration of premedication, immediately before anesthesia induction, which was assessed as laid out in the modified Yale Preoperative Anxiety Scale-Short Form (mYPAS-SF) [8] based on

End point values	ADV6209	Dormicum		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	40		
Units: 22,91-100				
median (inter-quartile range (Q1-Q3))	25 (23 to 37)	29 (23 to 40)		

Statistical analyses

Statistical analysis title	Mann Whitney U Test

Statistical analysis description:

Mann Whitney U Test

Comparison groups	ADV6209 v Dormicum

Number of subjects included in analysis	80
Analysis specification	Post-hoc
Analysis type	equivalence[1]
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)

Notes:

[1] - Anxiety scores obtained immediately prior to mask induction. This primary outcome parameter of the study did not reveal any statistical significance between the ADV6209 group and the conventional midazolam group.

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: overall trial	
Adverse event reporting additional description: clinical observation during the study	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Frequency threshold for reporting non-serious adverse events: 0 %

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: No non-serious adverse event related to the study medications were recorded.

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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

We included only children scheduled for anesthesia induction via facemask in this analysis, which could be considered as a limitation of the current study. This decision was based on the fact that anesthesia induction via facemask in children from

Notes: