



## Clinical trial results:

### Open-label Investigation of the Pharmacokinetic (PK) Profile, Safety, Tolerability, and Efficacy of Multiple Administrations of Tapentadol Oral Solution Used for Treatment of Acute Pain in Children Aged 2 Years to Less Than 7 Years.

#### Summary

EudraCT number	2019-000205-77
Trial protocol	PL
Global end of trial date	06 August 2020

#### Results information

Result version number	v1 (current)
This version publication date	08 January 2021
First version publication date	08 January 2021

#### Trial information

##### Trial identification

Sponsor protocol code	KF5503-75
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1225-7869

Notes:

#### Sponsors

Sponsor organisation name	Grünenthal GmbH
Sponsor organisation address	Zieglerstr. 6, Aachen, Germany, 52099
Public contact	Grünenthal Trial Information Desk, Grünenthal GmbH, 49 2415693223, Clinical-Trials@grunenthal.com
Scientific contact	Grünenthal Trial Information Desk, Grünenthal GmbH, 49 2415693223, Clinical-Trials@grunenthal.com

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?	Yes

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 August 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	06 August 2020
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To investigate the Pharmacokinetic (PK) profile of tapentadol after the administration of multiple doses of tapentadol oral solution to children aged 2 years to less than 7 years after a painful event that routinely produces acute pain requiring treatment with a strong analgesic medication (e.g., opioids or metamizole).

Protection of trial subjects:

The trial was conducted according to Good Clinical Practice guidelines, the applicable local laws, and in accordance with the ethical principles that have their origins in the Declaration of Helsinki. The competent authority approved the trial as required by national regulations. The regulatory authority was notified of the trial and amendments as required by national regulations. Tapentadol oral solution was administered to pediatric subjects in accordance with the approved SmPC for the pediatric population. Assessments/interventions have been limited as far as possible to those that would be performed according to the standard of care. Subjects were hospitalised during the entire treatment and evaluation phase to ensure the medical status of each subject was regularly and carefully monitored by qualified medical professionals. Vital signs (respiratory rate, blood pressure, and heart rate) and oxygen saturation (by pulse oximetry) were monitored as per local standard of care from before the administration of Dose 1 until the end of Visit 3. Vital signs and oxygen saturation values were recorded at specified time points before each investigational medicinal product administration and PK blood sampling.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 September 2019
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	Poland: 10
Worldwide total number of subjects	10
EEA total number of subjects	10

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)	10
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 study was conducted at 3 sites in Poland between 9 September 2019 and 06 August 2020.

### Pre-assignment

Screening details:

A total of 10 subjects were enrolled and treated in the study.

### Period 1

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

### Arms

<b>Arm title</b>	Tapentadol Oral Solution
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Arm description:

Subjects received a target dose of 1.25 milligram (mg) tapentadol per kilogram (kg) body weight every 4 hours ( $\pm$  15 minutes), in 1 of 2 available concentrations. Subjects with body weight less than or equal to ( $\leq$ ) 16 kg received tapentadol oral solution 4 milligram per milliliter (mg/mL); whereas subjects with body weight greater than ( $>$ ) 16 kg received tapentadol oral solution 20 mg/mL.

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

Dosage and administration details:

Subjects with body weight  $\leq$  16 kg received tapentadol oral solution 4 mg/mL; whereas subjects with body weight  $>$  16 kg received tapentadol oral solution 20 mg/mL.

Number of subjects in period 1	Tapentadol Oral Solution
Started	10
Completed	10

## Baseline characteristics

### Reporting groups

Reporting group title	Overall Study
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Reporting group description:

Subjects received a target dose of 1.25 mg tapentadol per kg body weight every 4 hours ( $\pm$  15 minutes), in 1 of 2 available concentrations. Subjects with body weight  $\leq$  16 kg received tapentadol oral solution 4 mg/mL; whereas subjects with body weight  $>16$  kg received tapentadol oral solution 20 mg/mL.

Reporting group values	Overall Study	Total	
Number of subjects	10	10	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	3.8 $\pm$ 1.8	-	
Gender categorical Units: Subjects			
Female	1	1	
Male	9	9	
Race Units: Subjects			
White	10	10	
American Indian Or Alaska Native	0	0	
Asian	0	0	
Black Or African American	0	0	
Native Hawaiian Or Other Pacific Islander	0	0	
Not Reported	0	0	
Other	0	0	

## End points

### End points reporting groups

Reporting group title	Tapentadol Oral Solution
Reporting group description:	
Subjects received a target dose of 1.25 milligram (mg) tapentadol per kilogram (kg) body weight every 4 hours ( $\pm$ 15 minutes), in 1 of 2 available concentrations. Subjects with body weight less than or equal to ( $\leq$ ) 16 kg received tapentadol oral solution 4 milligram per milliliter (mg/mL); whereas subjects with body weight greater than ( $>$ )16 kg received tapentadol oral solution 20 mg/mL.	

### Primary: Area Under the Concentration-Time Curve at Steady State for the Dosing Interval (AUC<sub>tau,SS</sub>) for Tapentadol

End point title	Area Under the Concentration-Time Curve at Steady State for the Dosing Interval (AUC <sub>tau,SS</sub> ) for Tapentadol <sup>[1]</sup>
End point description:	
AUC <sub>tau,SS</sub> was defined as area under the concentration-time curve at steady state for the dosing interval. The endpoint of this trial was estimated based on a population PK (popPK) model and the observed concentration-time data. The concentration data of all subjects who had a quantifiable serum concentration of tapentadol were analysed. The descriptive statistics presented for the endpoint include all evaluable subjects as per trial protocol.	
End point type	Primary
End point timeframe:	
Four-hour dosing interval at steady-state	

#### 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: Nonlinear mixed effects modeling approach using the first-order method with conditional estimation and interaction was applied to develop a popPK model based on the observed concentration-time data. The model was used to provide estimates of population and individual PK parameters and to simulate full multiple-dose concentration-time profiles for each subject based on the Empirical Bayes Estimates. The AUC<sub>tau,SS</sub> was calculated from the individual full profiles using the linear trapezoidal method.

<b>End point values</b>	Tapentadol Oral Solution			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: hour*nanogram per milliliter (h*ng/ml)				
arithmetic mean (standard deviation)	234.96 ( $\pm$ 51.45)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Area Under the Concentration-Time Curve at Steady State for the Dosing Interval (AUC<sub>tau,SS</sub>) for Tapentadol-O-Glucuronide

End point title	Area Under the Concentration-Time Curve at Steady State for the Dosing Interval (AUC <sub>tau,SS</sub> ) for Tapentadol-O-Glucuronide
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#### End point description:

Tapentadol-O-Glucuronide was the metabolite of Tapentadol. AUC<sub>tau,SS</sub> was defined as area under the

concentration-time curve at steady state for the dosing interval. The endpoint of this trial was estimated based on a popPK model and the observed concentration-time data. The concentration data of all subjects who had a quantifiable serum concentration of tapentadol-O-glucuronide were analysed. The descriptive statistics presented for the endpoint include all evaluable subjects as per trial protocol.

End point type	Secondary
End point timeframe:	
Four-hour dosing interval at steady-state	

<b>End point values</b>	Tapentadol Oral Solution			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: h*ng/ml				
arithmetic mean (standard deviation)	5829.38 ( $\pm$ 1000.07)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Area Under the Concentration-Time Curve at Steady State for the Dosing Interval (AUC<sub>tau,SS</sub>) for Tapentadol-O-Sulphate

End point title	Area Under the Concentration-Time Curve at Steady State for the Dosing Interval (AUC <sub>tau,SS</sub> ) for Tapentadol-O-Sulphate
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End point description:

Tapentadol-O-Sulphate was the metabolite of Tapentadol. AUC<sub>tau,SS</sub> was defined as area under the concentration-time curve at steady state for the dosing interval. The endpoint of this trial was estimated based on a popPK model and the observed concentration-time data. The concentration data of all subjects who had a quantifiable serum concentration of tapentadol-O-sulphate were analysed. The descriptive statistics presented for the endpoint include all evaluable subjects as per trial protocol.

End point type	Secondary
End point timeframe:	
Four-hour dosing interval at steady-state	

<b>End point values</b>	Tapentadol Oral Solution			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: h*ng/ml				
arithmetic mean (standard deviation)	334.51 ( $\pm$ 138.33)			

## Statistical analyses





## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Any adverse event (AE) that occurred between Dose 1 (included) until final dose + 48 hours (included), i.e. treatment emergent AE.

Adverse event reporting additional description:

Reported AE were treatment emergent AEs i.e. any AE that occurred between Dose 1 until final dose + 48 hour (included). Analysis was performed on safety analysis set that included all subjects with at least 1 investigational medicinal product administration.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.0
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### Reporting groups

Reporting group title	Tapentadol Oral Solution
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Reporting group description:

Subjects received a target dose of 1.25 mg tapentadol per kg body weight every 4 hours ( $\pm$  15 minutes), in 1 of 2 available concentrations. Subjects with body weight  $\leq$  16 kg received tapentadol oral solution 4 mg/mL; whereas subjects with body weight  $>16$  kg received tapentadol oral solution 20 mg/mL.

Serious adverse events	Tapentadol Oral Solution		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

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

Non-serious adverse events	Tapentadol Oral Solution		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 10 (50.00%)		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		

Regurgitation			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	2		
Vomiting			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	1 / 10 (10.00%)		
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? No

### **Limitations and caveats**

None reported