



Clinical trial results:

A blinded randomised placebo-controlled trial investigating the efficacy of morphine analgesia for procedural pain in infants

Summary

EudraCT number	2014-003237-25
Trial protocol	GB
Global end of trial date	05 June 2018

Results information

Result version number	v1 (current)
This version publication date	28 September 2018
First version publication date	28 September 2018

Trial information

Trial identification

Sponsor protocol code	POPPIV4.022.07.16
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Additional study identifiers

ISRCTN number	ISRCTN82342359
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	EudraCT Number: 2014-003237-25

Notes:

Sponsors

Sponsor organisation name	University of Oxford
Sponsor organisation address	CTRG, Research Services, Joint Research Office, Churchill Hospital, Oxford, United Kingdom, OX3 7LE
Public contact	Ms Heather House, University of Oxford, +44 01865572224, heather.house@admin.ox.ac.uk
Scientific contact	Ms Heather House, University of Oxford, +44 01865572224, heather.house@admin.ox.ac.uk

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	05 June 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 June 2018
Global end of trial reached?	Yes
Global end of trial date	05 June 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To test whether administration of morphine reduces clinical pain scores (PIPP-R) compared with a placebo (inactive solution) 30 seconds after an eye examination to test for retinopathy of prematurity (ROP).

To test whether administration of morphine reduces pain-related brain activity compared with a placebo (inactive solution) following a clinically-essential heel lance.

Protection of trial subjects:

Clinical stability was assessed throughout the 48-hour trial period (24 hours before and after the clinical intervention). These measures were calculated from pulse oximetry recordings and requirement for respiratory support. Pulse oximetry data were monitored and downloaded to the data logging equipment for 24 hours before and 24 hours after the start of the clinical intervention. Throughout the 48-hour trial period, blood pressure was monitored 6 hourly and changes in respiratory support (including type of respiratory support modality and oxygen requirement) were recorded.

Drug safety was assessed by measuring the number of occurrences of apnoea that required intervention using NeoPuff or 'bag and mask', or hypotension that required treatment with inotropes in the 24-hour period after drug administration. The DMC planned to review trial safety outcomes after every 25 patients had been randomised and safety data collected (i.e. n=25, 50, 75, 100 and 125). In addition, the Chief Investigator (or suitably trained delegate) was notified of every such occurrence.

A formal sequential safety procedure was applied and presented to the DMC for occurrences of apnoea that required intervention using NeoPuff or 'bag and mask'. We employed a stopping boundary using group sequential methods with a boundary agreed by the DMC and specified in the DMC Charter.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 September 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 31
Worldwide total number of subjects	31
EEA total number of subjects	31

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	31
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)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment to the trial began on 16th September 2016 and the last participant was recruited on 17 November 2017.

Pre-assignment

Screening details:

No screening data was collected.

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, Monitor, Carer, Assessor

Blinding implementation details:

Morphine sulphate and placebo solutions were delivered to the pharmacy in 10ml glass amber bottles with tamper-evident caps and a pack ID label, and dispensed to the Neonatal Unit. The solutions were indistinguishable by colour, odour and flow. Enrolment and randomisation of participants to a pack ID was carried out by the research team, using a web-based facility. The research team, clinical team, outcome assessors, infants and parents were masked to treatment allocation.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use, Nasogastric use

Dosage and administration details:

The volume of the dose of 100µg/kg of placebo (of equivalent volume) was calculated using the infant's working weight (the most recent weight documented in the infant's medical notes and used by the clinical team on their current drug prescription chart) and administered orally or via a nasogastric tube approximately 60 minutes prior to the heel lance.

Arm title	Morphine sulphate
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Morphine sulphate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Nasogastric use , Oral use

Dosage and administration details:

The volume of the dose of 100µg/kg of morphine sulphate (of equivalent volume) was calculated using the infant's working weight (the most recent weight documented in the infant's medical notes and used by the clinical team on their current drug prescription chart) and administered orally or via a nasogastric tube approximately 60 minutes prior to the heel lance.

Number of subjects in period 1	Placebo	Morphine sulphate
Started	16	15
Completed	15	15
Not completed	1	0
Consent withdrawn by subject	1	-

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Morphine sulphate
Reporting group description: -	

Reporting group values	Placebo	Morphine sulphate	Total
Number of subjects	16	15	31
Age categorical			
Gestational age at birth (weeks)			
Units: Subjects			
< 28+0 weeks	6	7	13
28+0 weeks or greater	9	8	17
Not recorded	1	0	1
Age continuous			
Gestational age at birth (weeks)			
Units: weeks			
median	28.6	28.1	
inter-quartile range (Q1-Q3)	27.9 to 29.7	26.3 to 30.1	-
Gender categorical			
Units: Subjects			
Female	7	3	10
Male	8	12	20
Not recorded	1	0	1
Gestational age at randomisation (weeks)			
Units: Subjects			
34+0 to 35+6 weeks	12	14	26
36+0 to 37+6 weeks	2	0	2
38+0 to 39+6 weeks	1	1	2
40+0 to 42+6 weeks	0	0	0
Not recorded	1	0	1
Mode of delivery			
Units: Subjects			
Spontaneous vaginal delivery	5	8	13
Assisted delivery	0	0	0
Caesarean section (elective or emergency)	10	7	17
Other	0	0	0
Not recorded	1	0	1
Days ventilated at randomisation			
Units: Subjects			
0 days	3	9	12
1 to < 7 days	8	2	10
7 or more days	4	4	8
Not recorded	1	0	1
Days since morphine was given			

Units: Subjects			
No morphine given	8	11	19
< 3 days	0	0	0
3 to < 7 days	1	0	1
7 or more days	6	4	10
Not recorded	1	0	1
Presence of gastric tube at randomisation			
Units: Subjects			
Yes	15	14	29
No	0	1	1
Not recorded	1	0	1
Intrauterine growth restriction			
Units: Subjects			
Yes	3	2	5
No	12	13	25
Not recorded	1	0	1
Baby has had surgery			
Units: Subjects			
Yes	1	0	1
No	14	15	29
Not recorded	1	0	1
Intraventricular haemorrhage (IVH) Grade I/II			
Units: Subjects			
Yes	3	2	5
No	12	13	25
Not recorded	1	0	1
Baby is one of a multiple pregnancy			
Units: Subjects			
Yes	4	4	8
No	11	11	22
Not recorded	1	0	1
Conceived using IVF treatment			
Units: Subjects			
Yes	0	1	1
No	15	14	29
Not recorded	1	0	1
Gestational age at randomisation (weeks)			
Units: Weeks			
median	34.7	34.7	
inter-quartile range (Q1-Q3)	34.1 to 35.1	34.1 to 35.1	-
Birth weight			
Units: Grams			
arithmetic mean	1173.4	1107.0	
standard deviation	± 349.5	± 328.7	-
Birth weight z-score (adjusted for sex and gestational age at birth)			
Units: standard deviations			
arithmetic mean	-0.2	-0.4	
standard deviation	± 1.0	± 0.9	-
Weight at randomisation			

Units: Grams arithmetic mean standard deviation	2130.7 ± 331.5	2048.5 ± 425.9	-
Apgar score at 10 minutes of age Units: Score median inter-quartile range (Q1-Q3)	10 8 to 10	10 9 to 10	-
Days ventilated at randomisation Units: Days median inter-quartile range (Q1-Q3)	3.5 2.0 to 19.5	8.0 1.0 to 20.0	-
Days since morphine was given Units: Days median inter-quartile range (Q1-Q3)	19.0 15.0 to 39.0	46.5 33.5 to 49.0	-

Subject analysis sets

Subject analysis set title	Per protocol population - Placebo arm
Subject analysis set type	Per protocol

Subject analysis set description:

The per-protocol population is infants randomised who received both the study treatment and the clinical intervention (heel lance followed by ROP screening), excluding post-randomisation exclusions. Baseline characteristics are reported for all infants randomised for whom data are available, excluding post-randomisation exclusions.

The following will be excluded from the per-protocol analysis population post-randomisation:

- Participants who did not receive the study treatment
- Participants who did not receive the clinical intervention (heel lance followed by ROP screening)
- Participants randomised in error
- Participants for whom full consent was not obtained
- Participants for whom consent to use their data was withdrawn by the parent(s)
- Participants for whom an entire record of fraudulent data was detected.

This group excludes the 1 baby for whom consent was withdrawn, who did not receive the treatment or clinical intervention.

Subject analysis set title	Per protocol population - Morphine arm
Subject analysis set type	Per protocol

Subject analysis set description:

The per-protocol population is infants randomised who received both the study treatment and the clinical intervention (heel lance followed by ROP screening), excluding post-randomisation exclusions. Baseline characteristics are reported for all infants randomised for whom data are available, excluding post-randomisation exclusions.

The following will be excluded from the per-protocol analysis population post-randomisation:

- Participants who did not receive the study treatment
- Participants who did not receive the clinical intervention (heel lance followed by ROP screening)
- Participants randomised in error
- Participants for whom full consent was not obtained
- Participants for whom consent to use their data was withdrawn by the parent(s)
- Participants for whom an entire record of fraudulent data was detected.

No babies were excluded from the morphine arm.

Reporting group values	Per protocol population - Placebo arm	Per protocol population - Morphine arm	
Number of subjects	15	15	

Age categorical			
Gestational age at birth (weeks)			
Units: Subjects			
< 28+0 weeks	6	7	
28+0 weeks or greater	9	8	
Not recorded	0	0	
Age continuous			
Gestational age at birth (weeks)			
Units: weeks			
median	28.6	28.1	
inter-quartile range (Q1-Q3)	27.9 to 29.7	26.3 to 30.1	
Gender categorical			
Units: Subjects			
Female	7	3	
Male	8	12	
Not recorded	0	0	
Gestational age at randomisation (weeks)			
Units: Subjects			
34+0 to 35+6 weeks	12	14	
36+0 to 37+6 weeks	2	0	
38+0 to 39+6 weeks	1	1	
40+0 to 42+6 weeks	0	0	
Not recorded	0	0	
Mode of delivery			
Units: Subjects			
Spontaneous vaginal delivery	5	8	
Assisted delivery	0	0	
Caesarean section (elective or emergency)	10	7	
Other	0	0	
Not recorded	0	0	
Days ventilated at randomisation			
Units: Subjects			
0 days	3	9	
1 to < 7 days	8	2	
7 or more days	4	4	
Not recorded	0	0	
Days since morphine was given			
Units: Subjects			
No morphine given	8	11	
< 3 days	0	0	
3 to < 7 days	1	0	
7 or more days	6	4	
Not recorded	0	0	
Presence of gastric tube at randomisation			
Units: Subjects			
Yes	15	14	
No	0	1	
Not recorded	0	0	
Intrauterine growth restriction			

Units: Subjects			
Yes	3	2	
No	12	13	
Not recorded	0	0	
Baby has had surgery			
Units: Subjects			
Yes	1	0	
No	14	15	
Not recorded	0	0	
Intraventricular haemorrhage (IVH) Grade I/II			
Units: Subjects			
Yes	3	2	
No	12	13	
Not recorded	0	0	
Baby is one of a multiple pregnancy			
Units: Subjects			
Yes	4	4	
No	11	11	
Not recorded	0	0	
Conceived using IVF treatment			
Units: Subjects			
Yes	0	1	
No	15	14	
Not recorded	0	0	
Gestational age at randomisation (weeks)			
Units: Weeks			
median			
inter-quartile range (Q1-Q3)			
Birth weight			
Units: Grams			
arithmetic mean			
standard deviation	±	±	
Birth weight z-score (adjusted for sex and gestational age at birth)			
Units: standard deviations			
arithmetic mean			
standard deviation	±	±	
Weight at randomisation			
Units: Grams			
arithmetic mean			
standard deviation	±	±	
Apgar score at 10 minutes of age			
Units: Score			
median			
inter-quartile range (Q1-Q3)			
Days ventilated at randomisation			
Units: Days			
median			
inter-quartile range (Q1-Q3)			
Days since morphine was given			

Units: Days			
median			
inter-quartile range (Q1-Q3)			

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Morphine sulphate
Reporting group description: -	
Subject analysis set title	Per protocol population - Placebo arm
Subject analysis set type	Per protocol

Subject analysis set description:

The per-protocol population is infants randomised who received both the study treatment and the clinical intervention (heel lance followed by ROP screening), excluding post-randomisation exclusions. Baseline characteristics are reported for all infants randomised for whom data are available, excluding post-randomisation exclusions.

The following will be excluded from the per-protocol analysis population post-randomisation:

- Participants who did not receive the study treatment
- Participants who did not receive the clinical intervention (heel lance followed by ROP screening)
- Participants randomised in error
- Participants for whom full consent was not obtained
- Participants for whom consent to use their data was withdrawn by the parent(s)
- Participants for whom an entire record of fraudulent data was detected.

This group excludes the 1 baby for whom consent was withdrawn, who did not receive the treatment or clinical intervention.

Subject analysis set title	Per protocol population - Morphine arm
Subject analysis set type	Per protocol

Subject analysis set description:

The per-protocol population is infants randomised who received both the study treatment and the clinical intervention (heel lance followed by ROP screening), excluding post-randomisation exclusions. Baseline characteristics are reported for all infants randomised for whom data are available, excluding post-randomisation exclusions.

The following will be excluded from the per-protocol analysis population post-randomisation:

- Participants who did not receive the study treatment
- Participants who did not receive the clinical intervention (heel lance followed by ROP screening)
- Participants randomised in error
- Participants for whom full consent was not obtained
- Participants for whom consent to use their data was withdrawn by the parent(s)
- Participants for whom an entire record of fraudulent data was detected.

No babies were excluded from the morphine arm.

Primary: PIPP-R score 30 seconds after ROP screening

End point title	PIPP-R score 30 seconds after ROP screening
End point description:	

End point type	Primary
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End point timeframe:

30 seconds after ROP screening

End point values	Per protocol population - Placebo arm	Per protocol population - Morphine arm		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	15		
Units: Score				
arithmetic mean (standard deviation)	10.5 (± 3.4)	11.1 (± 3.2)		

Statistical analyses

Statistical analysis title	Mean difference
Statistical analysis description:	
Unadjusted mean difference	
Comparison groups	Per protocol population - Placebo arm v Per protocol population - Morphine arm
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6634
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	3

Primary: Magnitude of nociceptive-specific brain activity evoked by heel lance

End point title	Magnitude of nociceptive-specific brain activity evoked by heel lance
End point description:	
End point type	Primary
End point timeframe:	
At heel lance (clinical intervention)	

End point values	Per protocol population - Placebo arm	Per protocol population - Morphine arm		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14 ^[1]	15		
Units: Projected weight of template				
median (inter-quartile range (Q1-Q3))	0.75 (0.33 to 1.22)	0.99 (0.40 to 1.56)		

Notes:

[1] - 1 missing

Statistical analyses

Statistical analysis title	Median difference
Statistical analysis description:	
Unadjusted median difference	
Comparison groups	Per protocol population - Placebo arm v Per protocol population - Morphine arm
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2474
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.16
upper limit	0.8

Secondary: PIPP-R score following heel lance

End point title	PIPP-R score following heel lance
End point description:	
End point type	Secondary
End point timeframe:	
30 second period after heel lance	

End point values	Per protocol population - Placebo arm	Per protocol population - Morphine arm		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	15		
Units: Score				
arithmetic mean (standard deviation)	8.5 (± 3.9)	7.9 (± 3.4)		

Statistical analyses

Statistical analysis title	Mean difference
Statistical analysis description:	
Unadjusted mean difference	
Comparison groups	Per protocol population - Placebo arm v Per protocol population - Morphine arm
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6571
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3
upper limit	2.1

Secondary: Amplitude of reflex withdrawal following heel lance

End point title	Amplitude of reflex withdrawal following heel lance
End point description:	
End point type	Secondary
End point timeframe:	
After heel lance	

End point values	Per protocol population - Placebo arm	Per protocol population - Morphine arm		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14 ^[2]	15		
Units: RMS activity				
median (inter-quartile range (Q1-Q3))	12.38 (6.11 to 46.33)	24.84 (19.66 to 44.84)		

Notes:

[2] - 1 missing

Statistical analyses

Statistical analysis title	Median difference
Statistical analysis description:	
Unadjusted median difference	
Comparison groups	Per protocol population - Placebo arm v Per protocol population - Morphine arm

Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4849
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	8.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.01
upper limit	22.39

Other pre-specified: Incidents of apnoea that require intervention using NeoPuff or 'bag and mask' in the 24-hour period following drug administration

End point title	Incidents of apnoea that require intervention using NeoPuff or 'bag and mask' in the 24-hour period following drug administration
End point description:	
Safety outcome	
End point type	Other pre-specified
End point timeframe:	
24-hour period following drug administration	

End point values	Per protocol population - Placebo arm	Per protocol population - Morphine arm		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	15		
Units: Infants				
>= 1	0	3		
None	15	12		

Statistical analyses

Statistical analysis title	Risk difference
Statistical analysis description:	
Unadjusted risk difference	
Comparison groups	Per protocol population - Morphine arm v Per protocol population - Placebo arm

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0528
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.4

Other pre-specified: Incidents of hypotension that require treatment with inotropes in the 24-hour period following drug administration

End point title	Incidents of hypotension that require treatment with inotropes in the 24-hour period following drug administration
End point description:	
Safety outcome	
End point type	Other pre-specified
End point timeframe:	
24-hour period following drug administration	

End point values	Per protocol population - Placebo arm	Per protocol population - Morphine arm		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	15		
Units: Infants	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

24 hours after study treatment administered

Assessment type	Systematic
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Dictionary used

Dictionary name	Not applicable
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Dictionary version	n/a
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Reporting groups

Reporting group title	Safety population - Placebo
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Reporting group description:

Safety analyses include all infants randomised who received the study treatment. In the placebo arm, one infant did not receive the study treatment and is excluded from this population.

Reporting group title	Safety population - Morphine
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Reporting group description:

Safety analyses includes all infants randomised who received the study treatment. In the morphine arm, all infants received the study treatment.

Serious adverse events	Safety population - Placebo	Safety population - Morphine	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)	2 / 15 (13.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Respiratory, thoracic and mediastinal disorders			
Apnoea			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Desaturations			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Safety population - Placebo	Safety population - Morphine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 15 (20.00%)	8 / 15 (53.33%)	
Respiratory, thoracic and mediastinal disorders			
Nasal congestion			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Desaturations			
subjects affected / exposed	1 / 15 (6.67%)	3 / 15 (20.00%)	
occurrences (all)	1	3	
Apnoea			
subjects affected / exposed	0 / 15 (0.00%)	5 / 15 (33.33%)	
occurrences (all)	0	5	
Skin and subcutaneous tissue disorders			
Perineal rash			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	

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.

The trial was terminated early after the predefined safety stopping boundary was crossed. This means that a smaller number of subjects was analysed than planned, and the study was under-powered.
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Notes: