Clinical trial results:
Pharmacokinetics of Intramuscular Adrenaline in Food-Allergic Teenagers
- does dose matter? The PIMAT study

Summary

EudraCT number	2017-003239-13
Trial protocol	GB
Global end of trial date	02 October 2018

Results information

Result version number	v1 (current)
This version publication date	06 June 2022
First version publication date	06 June 2022

Trial information

Trial identification

Sponsor protocol code	PIMAT

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03366298
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Imperial College London
Sponsor organisation address	Norfolk Place, London, United Kingdom, W2 1PG
Public contact	Turner, IMPERIAL COLLEGE LONDON, 44 02033127754, p.turner@imperial.ac.uk
Scientific contact	Turner, IMPERIAL COLLEGE LONDON, 44 02033127754, p.turner@imperial.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 April 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 October 2018
Global end of trial reached?	Yes
Global end of trial date	02 October 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effect of intramuscular self-injection of 300mcg and 500mcg adrenaline on blood levels of adrenaline ("pharmacokinetics") and the effect on the heart (blood pressure, heart rate, cardiac output), in food-allergic teenagers over 40kg, using an auto-injector device.

Protection of trial subjects:

Local anaesthetic cream for intravenous cannulation, supportive environment in paediatric research unit

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 November 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	United Kingdom: 12
Worldwide total number of subjects	12
EEA total number of subjects	0

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)	12
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening conducted according to protocol. 12 participants screened, all recruited

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	Investigator, Monitor, Subject, Data analyst, Assessor

Blinding implementation details:

Emerade devices were blinded in terms of dose. EPipen device not blinded as impossible to do so.

Arms

Are arms mutually exclusive?	Yes
Arm title	Emerade 300 / Epipen 0.3mg / Emerade 500

Arm description:

Visit 1: Emerade 300mcg then Epipen 0.3mg Visit 2: Emerade 500mcg

Arm type	Experimental
Investigational medicinal product name	Emerade 300mcg adrenaline auto-injector
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

as per SMPC

Investigational medicinal product name	Emerade 500mcg adrenaline auto-injector
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

As per SMPC

Investigational medicinal product name	Epipen 0.3mg adrenaline auto-injector
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

as per SMPC

Arm title	Epipen 0.3mg / Emerade 300 / Emerade 500

Arm description:

Visit 1: Epipen 0.3mg then Emerade 300mcg
Visit 2: Emerade 500mcg

Arm type	Experimental

Investigational medicinal product name	Emerade 500mcg adrenaline auto-injector
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:
as per SMPC

Investigational medicinal product name	Emerade 300mcg adrenaline auto-injector
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:
as per SMPC

Investigational medicinal product name	Epipen 0.3mg adrenaline auto-injector
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:
as per SMPC

Arm title	Emerade 500 / Emerade 300 / Epipen 0.3mg

Arm description:
Visit 1: Emerade 500mcg
Visit 2: Emerade 300mcg then Epipen 0.3mg

Arm type	Experimental
Investigational medicinal product name	Epipen 0.3mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:
As per SMPC

Investigational medicinal product name	Emerade 300mcg adrenaline auto-injector
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:
as per SMPC

Investigational medicinal product name	Emerade 500mcg adrenaline auto-injector
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:
as per SMPC

Arm title	Emerade 500 / Epipen 0.3mg / Emerade 300

Arm description:
Visit 1: Emerade 500mcg Visit 2: Epipen 0.3mg then Emerade 300mcg

Arm type	Experimental

Investigational medicinal product name	Emerade 300mcg adrenaline auto-injector
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:
as per SMPC

Investigational medicinal product name	Emerade 500mcg adrenaline auto-injector
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:
As per SMPC

Investigational medicinal product name	Epipen 0.3mg adrenaline auto-injector
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:
as per SMPC

Number of subjects in period 1	Emerade 300 / Epipen 0.3mg / Emerade 500	Epipen 0.3mg / Emerade 300 / Emerade 500	Emerade 500 / Emerade 300 / Epipen 0.3mg
Started	3	3	3
Completed	3	3	3

Number of subjects in period 1	Emerade 500 / Epipen 0.3mg / Emerade 300
Started	3
Completed	3

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial
Reporting group description:	
12 subjects recruited, all of whom then participated in the crossover trial	

Reporting group values	Overall trial	Total	
Number of subjects	12	12	
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)	12	12	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
median	15.4		
full range (min-max)	13.3 to 18.3	-	
Gender categorical Units: Subjects			
Female	5	5	
Male	7	7	

End points

End points reporting groups

Reporting group title	Emerade 300 / Epipen 0.3mg / Emerade 500
Reporting group description: Visit 1: Emerade 300mcg then Epipen 0.3mg Visit 2: Emerade 500mcg	
Reporting group title	Epipen 0.3mg / Emerade 300 / Emerade 500
Reporting group description: Visit 1: Epipen 0.3mg then Emerade 300mcg Visit 2: Emerade 500mcg	
Reporting group title	Emerade 500 / Emerade 300 / Epipen 0.3mg
Reporting group description: Visit 1: Emerade 500mcg Visit 2: Emerade 300mcg then Epipen 0.3mg	
Reporting group title	Emerade 500 / Epipen 0.3mg / Emerade 300
Reporting group description: Visit 1: Emerade 500mcg Visit 2: Epipen 0.3mg then Emerade 300mcg	
Subject analysis set title	Emerade 300mcg
Subject analysis set type	Full analysis
Subject analysis set description: Emerade 300mmcg	
Subject analysis set title	Emerade 500mcg
Subject analysis set type	Full analysis
Subject analysis set description: Emerade 500mcg	
Subject analysis set title	Epipen 300
Subject analysis set type	Full analysis
Subject analysis set description: Epipen	

Primary: Plasma Catecholamine Levels (Maximum Concentration, Cmax)

End point title	Plasma Catecholamine Levels (Maximum Concentration, Cmax)
End point description: Pharmacokinetics (plasma catecholamine levels: Cmax) following intramuscular self-injection of 300mcg and 500mcg adrenaline using an auto-injector device, in food-allergic teenagers over 40kg.	
End point type	Primary
End point timeframe: Overall 0-180mins	

End point values	Emerade 300mcg	Emerade 500mcg	Epipen 300	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	12	12	12	
Units: pg/ml				
geometric mean (confidence interval 95%)	218 (132 to 359)	394 (310 to 500)	290 (200 to 421)	

Statistical analyses

Statistical analysis title	Peak plasma adrenaline concentration
Comparison groups	Emerade 300mcg v Emerade 500mcg
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	equivalence[1]
Parameter estimate	Bioequivalence comparison
Point estimate	1.53
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.05
upper limit	2.22

Notes:

[1] - Bioequivalence data (ratio of geometric mean with 90% confidence intervals):

Statistical analysis title	Peak plasma adrenaline concentration
Comparison groups	Emerade 300mcg v Epipen 300
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	equivalence[2]
Parameter estimate	Bioequivalence comparison
Point estimate	1.03
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.83
upper limit	1.29

Notes:

[2] - Bioequivalence data (ratio of geometric mean with 90% confidence intervals):

Statistical analysis title	Peak plasma adrenaline concentration
Comparison groups	Emerade 300mcg v Emerade 500mcg v Epipen 300
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[3]
Parameter estimate	Bioequivalence comparison
Point estimate	1.36
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.03
upper limit	1.78

Notes:

[3] - Bioequivalence data (ratio of geometric mean with 90% confidence intervals):

Primary: Plasma Catecholamine Levels (Time to Maximum Concentration, Tmax)	
End point title	Plasma Catecholamine Levels (Time to Maximum Concentration, Tmax)
End point description:	
Pharmacokinetics (plasma catecholamine levels: Tmax) following intramuscular self-injection of 300mcg and 500mcg adrenaline using an auto-injector device, in food-allergic teenagers over 40kg.	
End point type	Primary
End point timeframe:	
0-180 minutes	

End point values	Emerade 300mcg	Emerade 500mcg	Epipen 300	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	12	12	12	
Units: minutes				
geometric mean (confidence interval 95%)	9.6 (5.3 to 17.4)	8.5 (6.1 to 11.8)	5.9 (4.9 to 7.3)	

Statistical analyses

Statistical analysis title	Time to peak concentration (first peak)
Comparison groups	Emerade 300mcg v Emerade 500mcg
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	equivalence[4]
Parameter estimate	Bioequivalence comparison
Point estimate	0.88
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.51
upper limit	1.5

Notes:

[4] - Bioequivalence comparison, data are presented as ratio of geometric mean with 90% confidence intervals

Statistical analysis title	Time to peak concentration (first peak)
Comparison groups	Emerade 300mcg v Epipen 300

Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	equivalence[5]
Parameter estimate	Bioequivalence comparison
Point estimate	0.62
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.38
upper limit	1.01

Notes:

[5] - Bioequivalence comparison, data are presented as ratio of geometric mean with 90% confidence intervals

Statistical analysis title	Time to peak concentration (fir...
Comparison groups	Emerade 500mcg v Epipen 300
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	equivalence[6]
Parameter estimate	Bioequivalence comparison
Point estimate	1.43
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.06
upper limit	1.93

Notes:

[6] - Bioequivalence comparison, data are presented as ratio of geometric mean with 90% confidence intervals

Primary: Plasma Catecholamine Levels (Maximum Concentration, Area-under-curve (AUC))

End point title	Plasma Catecholamine Levels (Maximum Concentration, Area-under-curve (AUC))

End point description:

Pharmacokinetics (plasma catecholamine levels: AUC) following intramuscular self-injection of 300mcg and 500mcg adrenaline using an auto-injector device, in food-allergic teenagers over 40kg.

Baseline corrected.

End point type	Primary

End point timeframe:

0-180mins

End point values	Emerade 300mcg	Emerade 500mcg	Epipen 300	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	12	12	12	
Units: hr.pg/ml				
geometric mean (confidence interval 95%)	174 (86 to 354)	387 (263 to 570)	203 (142 to 292)	

Statistical analyses

Statistical analysis title	Area under Plasma adrenaline curve (AUC)
Statistical analysis description:	
Area under Plasma adrenaline curve (AUC) - baseline corrected, 0-180	
Comparison groups	Emerade 300mcg v Emerade 500mcg
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	equivalence[7]
Parameter estimate	Bioequivalence comparison
Point estimate	1.75
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.06
upper limit	2.88

Notes:

[7] - Bioequivalence comparison, data are presented as ratio of geometric mean with 90% confidence intervals

Statistical analysis title	Area under Plasma adrenaline curve (AUC)
Statistical analysis description:	
Area under Plasma adrenaline curve (AUC) - baseline corrected, 0-180	
Comparison groups	Emerade 300mcg v Epipen 300
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	equivalence[8]
Parameter estimate	Bioequivalence comparison
Point estimate	0.9
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.65
upper limit	1.24

Notes:

[8] - Bioequivalence comparison, data are presented as ratio of geometric mean with 90% confidence intervals

Statistical analysis title	Area under Plasma adrenaline cu...
Statistical analysis description:	
Area under Plasma adrenaline curve (AUC) - baseline corrected, 0-180	
Comparison groups	Emerade 500mcg v Epipen 300

Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	equivalence[9]
Parameter estimate	Bioequivalence comparison
Point estimate	1.9
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.41
upper limit	2.57

Notes:

[9] - Bioequivalence comparison, data are presented as ratio of geometric mean with 90% confidence intervals

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
1 day	
Adverse event reporting additional description:	
Adverse events following self-administration of adrenaline via autoinjector device defined as in protocol	
Assessment type	Systematic

Dictionary used	
Dictionary name	per protocol
Dictionary version	n/a

Reporting groups	
Reporting group title	Emerade 300mcg
Reporting group description: -	
Reporting group title	Emerade 500mcg
Reporting group description: -	
Reporting group title	Epipen 0.3mg
Reporting group description: -	

Serious adverse events	Emerade 300mcg	Emerade 500mcg	Epipen 0.3mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	Emerade 300mcg	Emerade 500mcg	Epipen 0.3mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 12 (66.67%)	9 / 12 (75.00%)	8 / 12 (66.67%)
Cardiac disorders			
Palpitations			
subjects affected / exposed	3 / 12 (25.00%)	4 / 12 (33.33%)	3 / 12 (25.00%)
occurrences (all)	3	4	3
Nervous system disorders			
Tremor			
subjects affected / exposed	3 / 12 (25.00%)	7 / 12 (58.33%)	8 / 12 (66.67%)
occurrences (all)	3	7	8
General disorders and administration site conditions			

Pain at injection site			
subjects affected / exposed	8 / 12 (66.67%)	6 / 12 (50.00%)	7 / 12 (58.33%)
occurrences (all)	8	6	7
Systemic AE (any)			
subjects affected / exposed	4 / 12 (33.33%)	9 / 12 (75.00%)	8 / 12 (66.67%)
occurrences (all)	4	9	8

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

None reported