LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Emerade
(adrenaline tartrate)

SE/H/1261/01–03/DC

This module reflects the scientific discussion for the approval of Emerade. The procedure was finalised at 2012-11-28. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

I. INTRODUCTION

Mimer Medical has applied for a marketing authorisation for Emerade, solution for injection in pre-filled pen, 150 microgram, 300 microgram and 500 microgram claiming essential similarity to EpiPen, solution for injection, 0.15 mg and 0.30 mg marketed in Sweden by Meda AB. The product contains adrenaline tartrate as active substance. For approved indications see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Emerade is presented in the form of a solution for injection containing adrenaline tartrate which is used to deliver doses corresponding to 150 microgram, 300 microgram and 500 microgram adrenaline. The excipients are disodium edetate, hydrochloric acid, sodium chloride, sodium metabisulfite and water. The solution for injection is filled in a pre-filled pen.

II.2 Drug Substance

Adrenaline tartrate has a monograph in the Ph Eur.

Adrenaline tartrate is a white or greyish-white crystalline powder which is freely soluble in water and slightly soluble in ethanol. The structure of adrenaline tartrate has been adequately proven and its physico-chemical properties sufficiently described. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Emerade, 150 micrograms, 300 micrograms and 500 micrograms, solution for injection in pre-filled pen is formulated using excipients described in the current Ph Eur. There are no raw materials of animal origin used in the product.

The product development has taken into consideration the physico-chemical characteristics of the active substance, such as the sensitivity for degradation by oxidation.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, when protected from freezing.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Emerade is an aqueous solution for intramuscular administration. Emerade contains the same active substance in the same concentration as the reference product, EpiPen. There are however a few differences between the Emerade and the EpiPen formulations. In Emerade the active substance is present as adrenaline tartrate while EpiPen contains the adrenaline base. The Emerade formulation also contains the chelating agent disodium EDTA which is not present in EpiPen. These formulation differences are not expected to affect the bioavailability of adrenaline.

Furthermore, the use of adrenaline tartrate is not considered to have any significant impact on safety and efficacy compared to the adrenaline base. The dose span for adrenaline products is relatively wide, due to high variability in response, and independent of the absorption. The use of adrenaline tartrate for both intramuscular and subcutaneous use is well-established and there are other products containing the salt approved within the EU.

In conclusion: The difference in composition between the formulations is not considered to affect the bioavailability of adrenaline and the absence of bioequivalence studies is acceptable.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was Czech.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The applicant responded satisfactorily to RMS questions regarding layout The PL for Emerade is considered as readable and comprehensible.

The risk/benefit ratio is considered positive and Emerade, 150 microgram, 300 microgram and 500 microgram, solution for injection in pre-filled pen is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Emerade, 150 microgram, 300 microgram and 500 microgram, solution for injection in pre-filled pen was successfully finalised on 2012-11-28.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
SE/H/1261/01-03/II/19	As a result of the Article 31 referral procedure for adrenaline auto-injectors (AAI), EMEA/H/A-31/1398, each Marketing Authorisation Holder of adrenaline auto-injectors were obligated to perform a PK/PD study to understand the influence of different factors on distribution, exposure and activity of adrenaline when administered via their adrenaline auto-injector device. With this variation application for Emerade, the MAH has submitted the results from one clinical trial evaluating PK and PD parameters of adrenaline: • Study N-A-PH1-15-050, a single dose, open label, randomized cross-over study to explore the pharmacokinetics and pharmacodynamics of epinephrine in healthy male and female subjects with different skin-to-muscle depth (STMD) of the thigh after injections with four different marketed auto-injectors.	Yes	2020-01-20	Approval	Please see separate report attached at the end of this PAR.

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
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Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

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With this variation application for Emerade, the MAH has submitted the results from one clinical trial evaluating PK and PD parameters of adrenaline:

- Study N-A-PH1-15-050, a single dose, open label, randomized cross-over study to explore the pharmacokinetics and pharmacodynamics of epinephrine in healthy male and female subjects with different skin-to-muscle depth (STMD) of the thigh after injections with four different marketed auto-injectors.

Study N-A-PH1-15-050

Study objectives

Primary Objective

- To assess the pharmacokinetics (PK) and pharmacodynamics (PD) of epinephrine with standard auto-injectors into the anterolateral thigh in healthy male and female subjects with a variety of compressed STMD.

Secondary Objectives

- To assess treatment related changes in the PD parameters heart rate and blood pressure.
- To compare in an exploratory way the PK and PD parameters between the different cohorts of male and female subjects with different compressed STMD.

Methods

Study design

Part 1:

The first part of the trial was an open label, randomized, two way cross-over trial in 8 healthy subjects (5 male and 3 female) with a compressed STMD of 10-20 mm to evaluate the PK of epinephrine (Suprarenin, 1 mg/ml, solution for injection) after subcutaneous (s.c.) and intramuscular (i.m.) injection antero-laterally in the thigh.

A single dose of 500 µg epinephrine (0.5 mL Suprarenin®) was administered i.m. and s.c. using a needle and a syringe in randomized order. Both treatment administrations occurred under ultrasound guidance: s.c. administration should have occurred at a depth of approximately 50% of the s.c. fatty tissue and i.m. administration should have occurred at a depth of approximately 25 mm. The following needles were used; for i.m. administration: 18 gauge, 50 mm; for s.c. administration: 27 gauge, 20 mm. The study periods were separated by a wash-out of at least 24 hours.

Part 2:

The second part of the trial was an open label, randomized, four way cross-over trial in 40 healthy subjects:16 in Cohort 1 and Cohort 2, each (8 male, 8 female) and 8 in Cohort 3 (0 male, 8 female) to evaluate the penetration and absorption of epinephrine after application of 4

different commercially available epinephrine auto-injectors after state of the art administration of epinephrine.

Subjects were stratified into cohorts for analysis based on the compressed lateral right thigh STMD lying within the following ranges:

- Cohort 1: compressed STMD ≥ 10, <15 mm
- Cohort 2: compressed STMD ≥ 15, ≤ 20 mm
- Cohort 3: compressed STMD > 20 mm

Each subject received 300 or 500 µg epinephrine administered with three different epinephrine auto-injectors in randomized order. Each dose of epinephrine was applied by trained staff using the four commercially available auto-injectors according to the instruction for each individual device. The study periods were separated by a wash-out of at least 24 hours.

In both part 1 and part 2, blood samples for analytical assay were collected pre-dose (-90, -60 and -30 minutes) and at 3, 5, 8, 10, 12, 15, 20, 25, 30, 40, 50, 60, 75, 90 minutes and 3 hours after each administration.

Blood pressure and pulse rate were measured pre-dose and at 5, 10, 15, 20, 30 minutes after each administration and thereafter every 15 minutes until 4 hours after dosing (45, 60, 75, 90, 105, 120, 135, 150, 165, 180, 195, 210, 225, 240 minutes after administration). ECG (heart rate) was recorded pre-dose and at 30, 60 minutes, 2 and 4 hours after each administration.

Treatments administered

Part 1:

- Investigational medicinal product (IMP) 1: Suprarenin®, 1 mg/ml epinephrine solution for injection (Sanofi-Aventis, Germany).

Part 2:

- Investigational medicinal product 2: 300 µg epinephrine auto-injector (Emerade®, Bausch and Lomb, 23 mm needle length)
- Investigational medicinal product 3: 500 µg epinephrine auto-injector (Emerade®, Bausch and Lomb, 23 mm needle length)
- Investigational medicinal product 4: 300 µg epinephrine auto-injector (“Product 4”, 16 mm needle length)
- Investigational medicinal product 5: 300 µg epinephrine auto-injector (“Product 5”, 15 mm needle length)

Study population

Part 1:
Overall 5 healthy male and 3 healthy female subjects, aged 25-53 years and with BMI 29.1-35.8 kg/m^2, were enrolled. Five subjects had STMD ≥ 10, <15 mm and 3 subjects STMD ≥ 15, ≤ 20 mm. All 8 subjects completed the study as planned.

Part 2:
40 healthy subjects, aged 21-54 years and with BMI 20.6-38.1 kg/m^2, were enrolled; 16 in Cohort 1 (8 male, 8 female), 16 subjects in Cohort 2 (8 male, 8 female) and 8 subjects in Cohort 3 (all female). A total of 35 subjects (15 in Cohort 1 [n=8 male, n=7 female]; 14 in Cohort 2 [n=8 male, n=6 female]; and 6 in Cohort 3 [all female]) completed Part 2. Overall, 5 subjects (1 in Cohort 1, 2 in Cohort 2, and 2 in Cohort 3, all female) were discontinued due to

adverse events (n=4) and for not meeting the inclusion criteria (n=1). Overall 38 subjects were included in the PK and PD analysis sets.

Results

Pharmacokinetic results

Mean base-line concentrations were approximately 17 pg/ml (range 15-75 pg/ml) across cohorts in part 1 and part 2, with no notable differences between treatment groups. This corresponds to approximately 5% of Cmax.

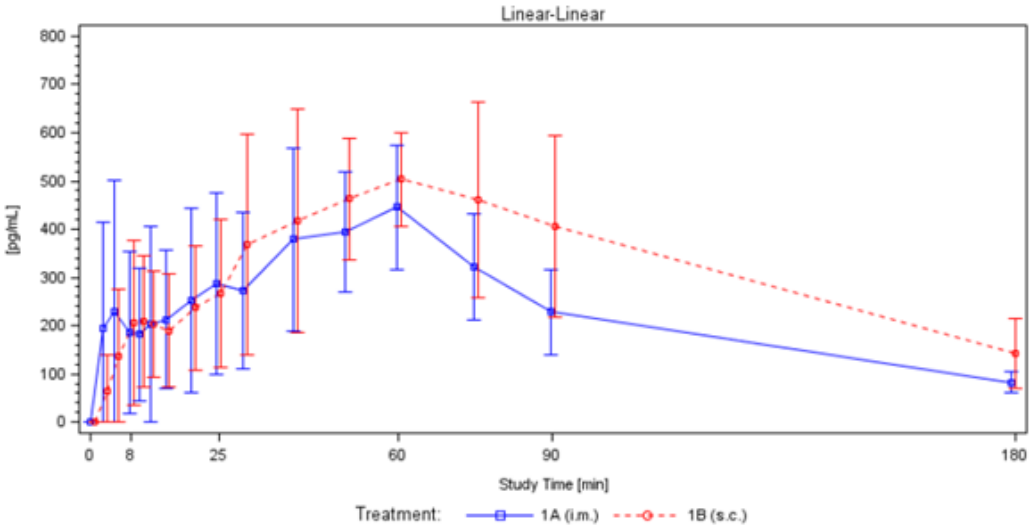
Part 1:

During the first 5 minutes after epinephrine administration, the baseline-corrected mean epinephrine plasma concentrations were higher after i.m. administration. Mean values in the i.m. and s.c. groups, respectively, were 194.3 pg/mL versus 62.94 pg/mL at 3 minutes post-dose and 228.5 pg/mL versus 137.3 pg/mL at 5 minutes post-dose. This corresponds to approximately 3-fold higher baseline corrected mean epinephrine plasma concentrations in the i.m. group at 3 minutes and 1.7-fold higher concentrations at 5 minutes post-dose, indicating slightly slower absorption in the s.c. group compared to i.m group.

Mean baseline-corrected plasma concentrations of epinephrine increased to reach a maximum around 60 minutes post-dose for both i.m. and s.c. administration groups and then decreased through the last sample at 180 minutes post-dose.

Baseline corrected adrenaline plasma concentration vs time profile are presented in Figure 1.

Figure 1. Adrenaline plasma concentration vs time profile, arithmetic mean ± SD. All Cohorts.



Treatment 1A=Suprarenin 500 µg, i.m., Treatment 1B= Suprarenin 500 µg, s.c.
Source: Figure 14.2.2.1.1.2.

In subjects with compressed STMD <15 mm (Cohort 1), baseline corrected mean epinephrine plasma concentrations were higher during the first 25 to 30 minutes after i.m. administration, with concentrations for the s.c. route exceeding those of the i.m. route after 30-minutes post dose (Figure 2). In Cohort 2 (STMD ≥15 and ≤20 mm), the baseline corrected mean

epinephrine plasma concentrations were consistently lower after i.m. compared to s.c. administration of the IMP, however differences were negligible at 60 and 75 minutes after dosing (Figure 3).

Figure 2. Mean plasma concentration time profiles of adrenaline, baseline corrected, Part 1, Cohort 1 (pg/ml). STMD < 15 mm.

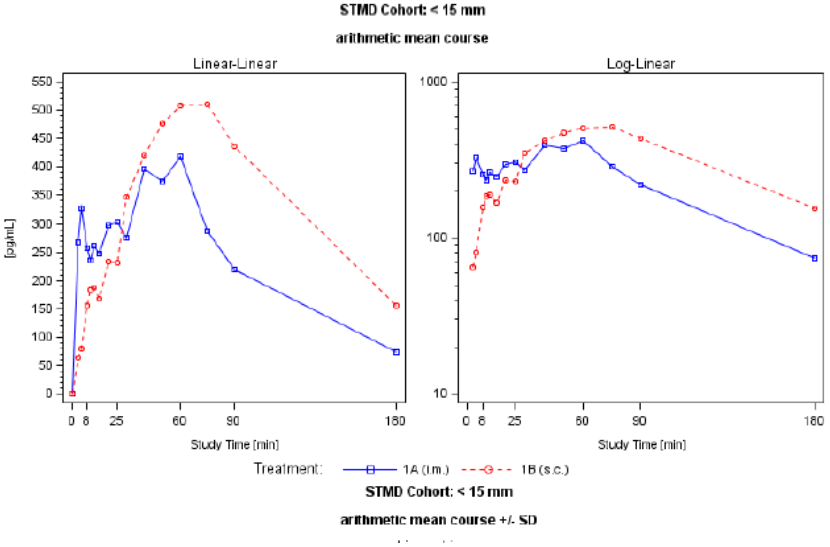
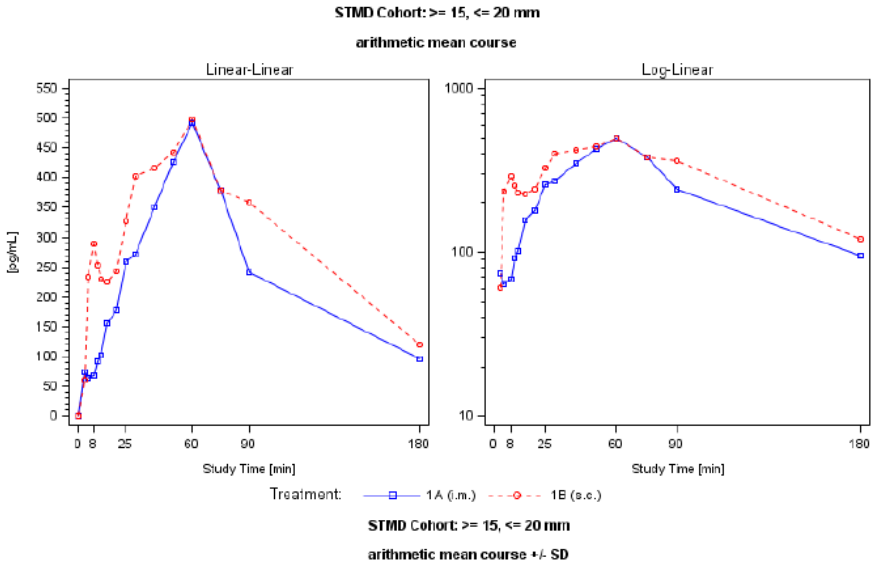


Figure 3. Mean plasma concentration time profiles of adrenaline, baseline corrected, Part 1, Cohort 2 (pg/ml). STMD ≥ 15 mm, ≤ 20 mm.



Part 2:

The following legends are used in the figures below:

- Treatment 1: Emerade, 300 µg auto-injector
- Treatment 2: Emerade, 500 µg auto-injector
- Treatment 3: “Product 4”, 300 µg auto-injector
- Treatment 4: “Product 5”, 300 µg auto-injector

During the first 5 minutes after epinephrine administration, the mean baseline-corrected epinephrine plasma concentrations increased rapidly with all investigational medicinal products and were highest (overall) after administration of ”Product 4” at 5 minutes post-dose. Mean values for Emerade 300, Emerade 500, ”Product 4” and ”Product 5”, respectively, were 96.76 pg/mL, 123.6 pg/mL, 119.6 pg/mL and 82.69 pg/mL at 3 minutes post-dose and 98.25 pg/mL, 145.4 pg/mL, 210.7 pg/mL and 150.2 pg/mL at 5 minutes post-dose. This corresponds to approximately 1.4- to 2.1-fold higher baseline corrected mean epinephrine plasma concentrations after ”Product 4” at 5 minutes post-dose. Mean baseline corrected plasma concentrations are displayed up to 180 minutes and up to 10 minutes after drug administration in the figures below.

In cohort 1 (subjects with STMD < 15 mm) mean epinephrine concentrations displayed two peaks. An initial early peak was observed in the first 5 mins, and a second peak was observed between 40 and 60 mins (Figure 4). The double peaks were less pronounced in cohort 2 and 3 (Figure 5 and Figure 6).

Figure 4. Mean plasma concentration time profiles of adrenaline (pg/ml) by treatment and STMD Cohort, baseline corrected, Part 2. STMD Cohort <15 mm.

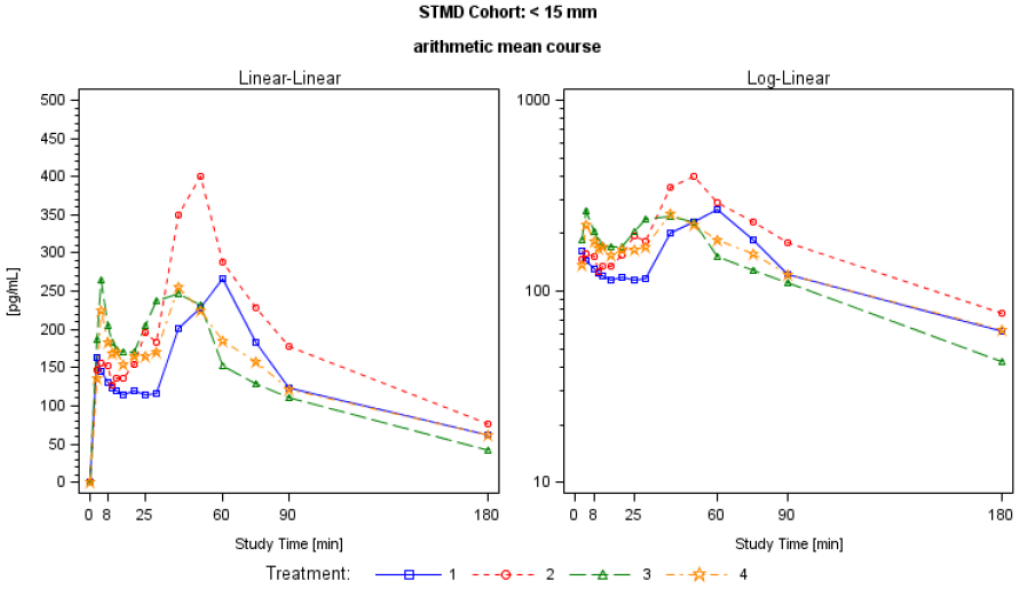


Figure 5. Mean plasma concentration time profiles of adrenaline (pg/ml) by treatment and STMD Cohort, baseline corrected, Part 2. STMD Cohort ≥15 mm, ≤ 20 mm.

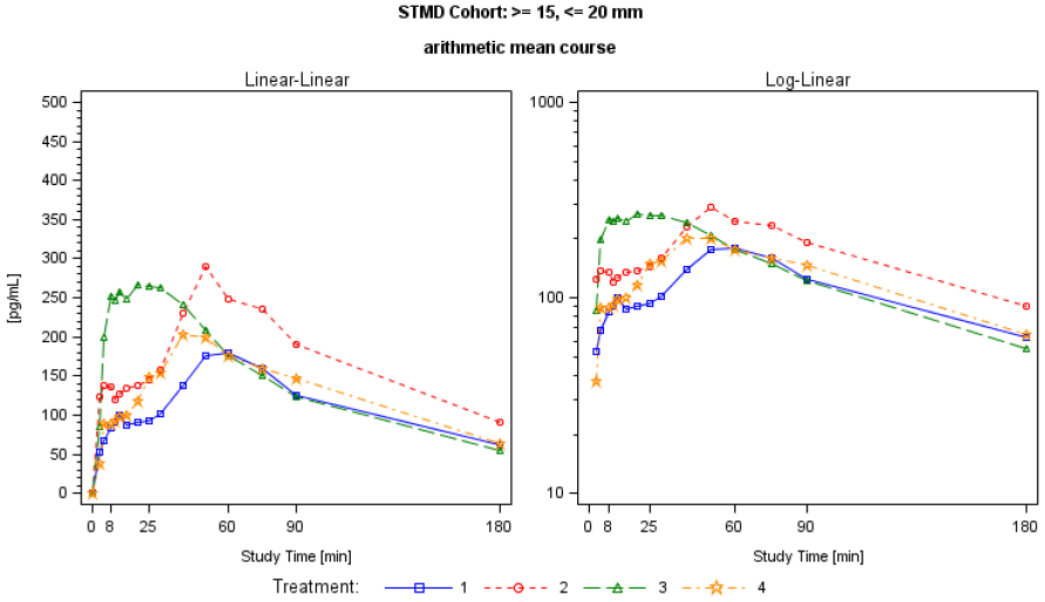


Figure 6. Mean plasma concentration time profiles of adrenaline (pg/ml) by treatment and STMD Cohort, baseline corrected, Part 2. STMD Cohort > 20 mm.

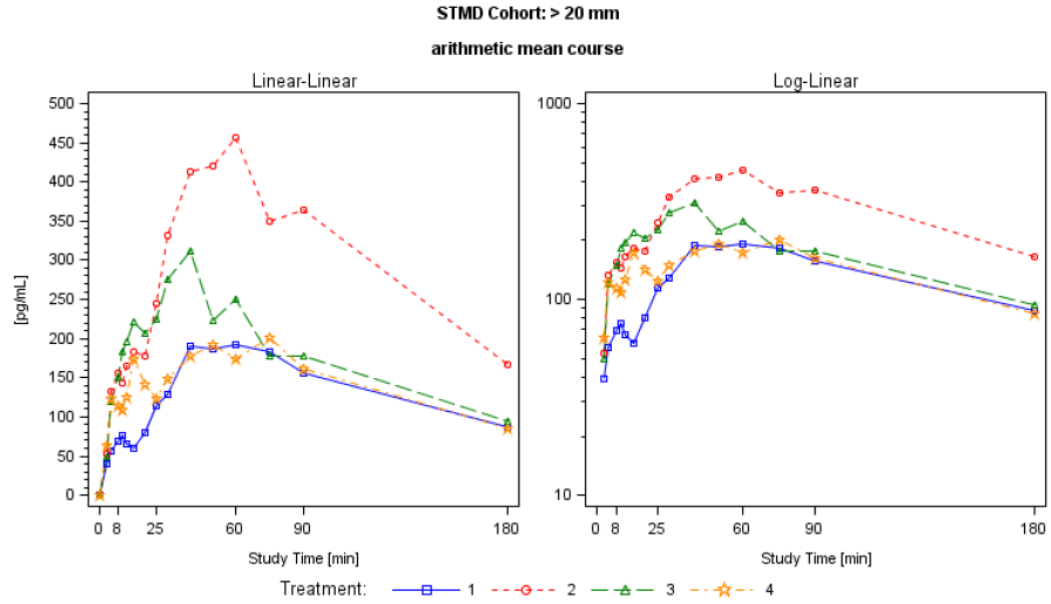


Figure 7. Mean plasma concentration time profiles of adrenaline (pg/ml) by treatment and STMD Cohort until 10 minutes, baseline corrected, Part 2. STMD Cohort <15 mm.

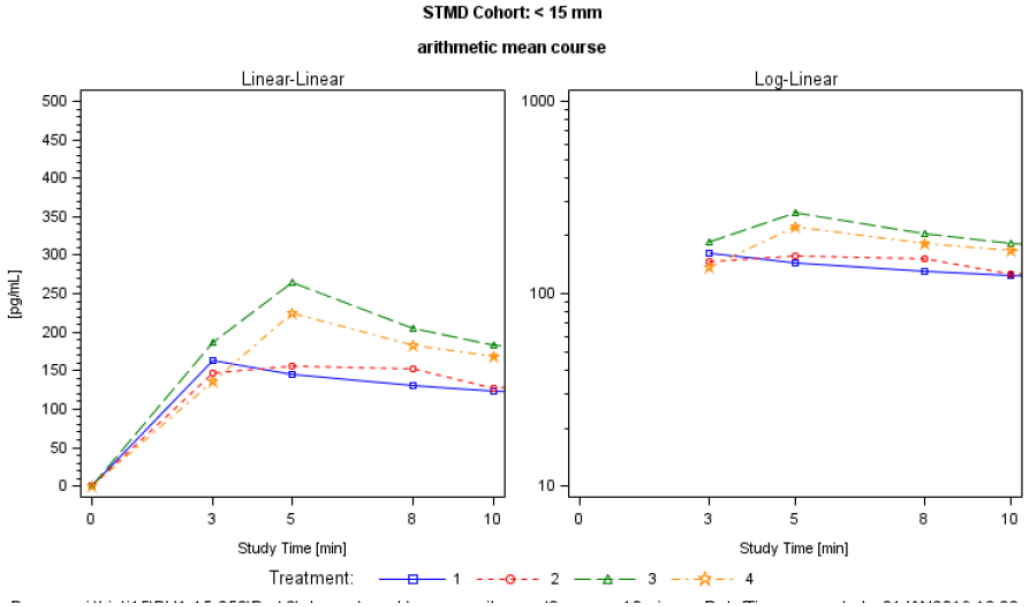


Figure 8. Mean plasma concentration time profiles of adrenaline (pg/ml) by treatment and STMD Cohort until 10 minutes, baseline corrected, Part 2. STMD Cohort ≥15 mm, ≤ 20 mm.

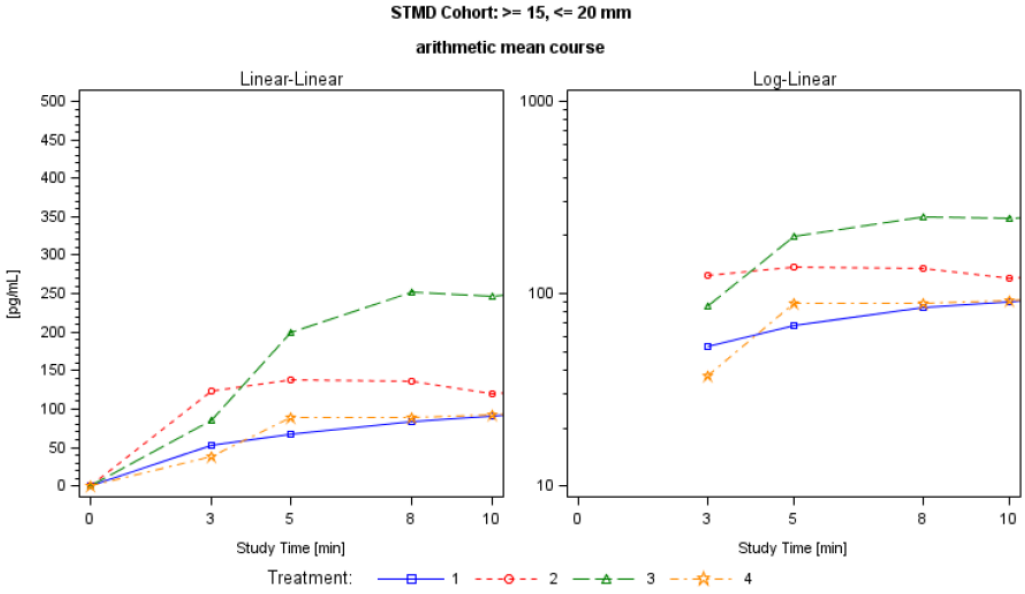
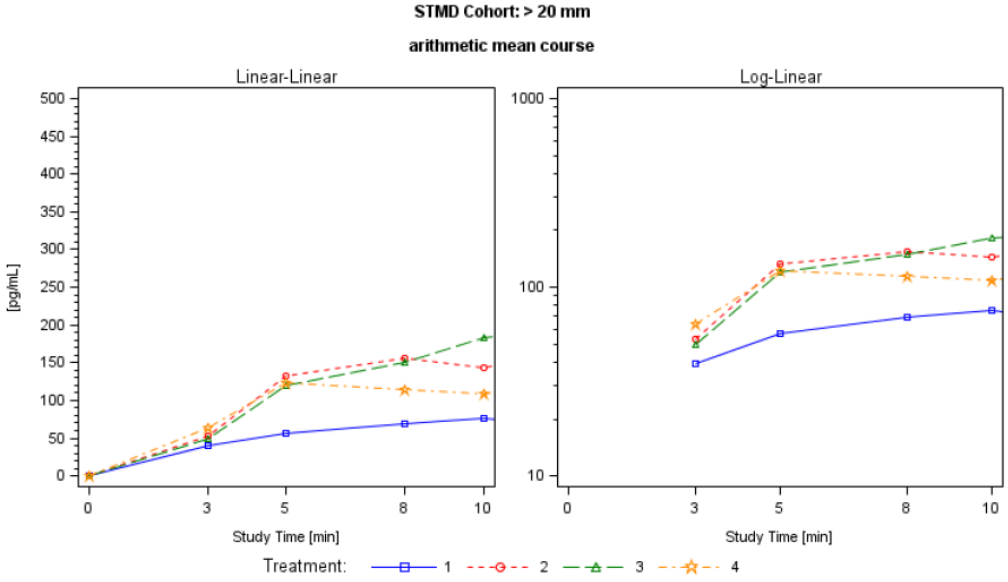


Figure 9. Mean plasma concentration time profiles of adrenaline (pg/ml) by treatment and STMD Cohort until 10 minutes, baseline corrected, Part 2. STMD Cohort > 20 mm.



With regards to sex, Cohort 2, mean plasma concentration profiles were similar for male and female subjects (Figure 11), given the variability at each point. However, higher baseline corrected epinephrine peak plasma concentrations were observed in male subjects of Cohort 1 (Figure 10) for all IMP treatments administered, although the immediate initial peak (first 10 minutes) appeared higher for mean females compared to mean males. Since only female subjects were included on Cohort 3, no comparison of the profiles with male subjects was possible for this cohort.

Figure 10. Mean plasma concentration time profiles of adrenaline up to 180 minutes, baseline corrected, Part 2, Cohort 1, by sex (pg/ml). STMD Cohort < 15 mm, male (upper panel), female (lower panel).

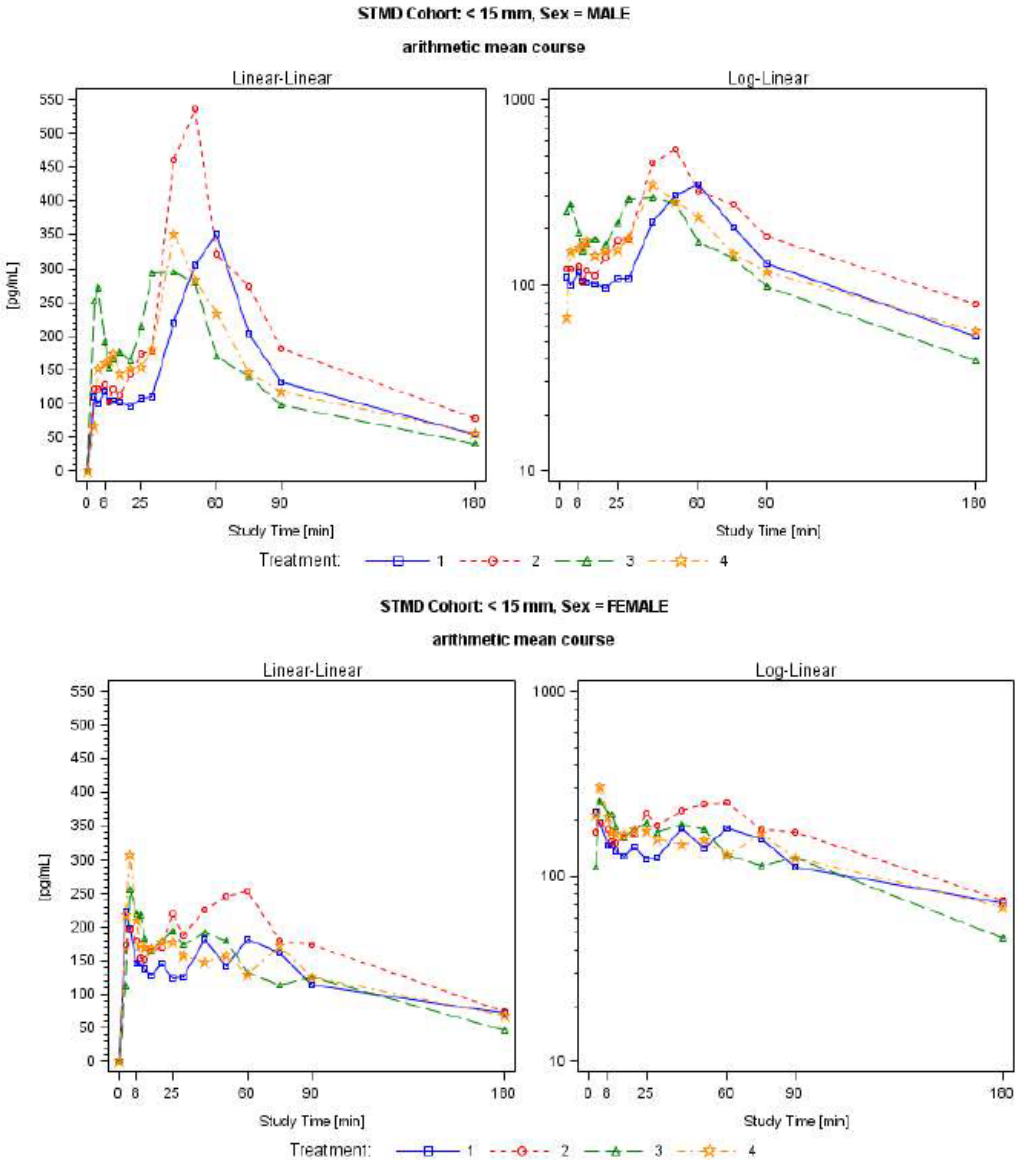
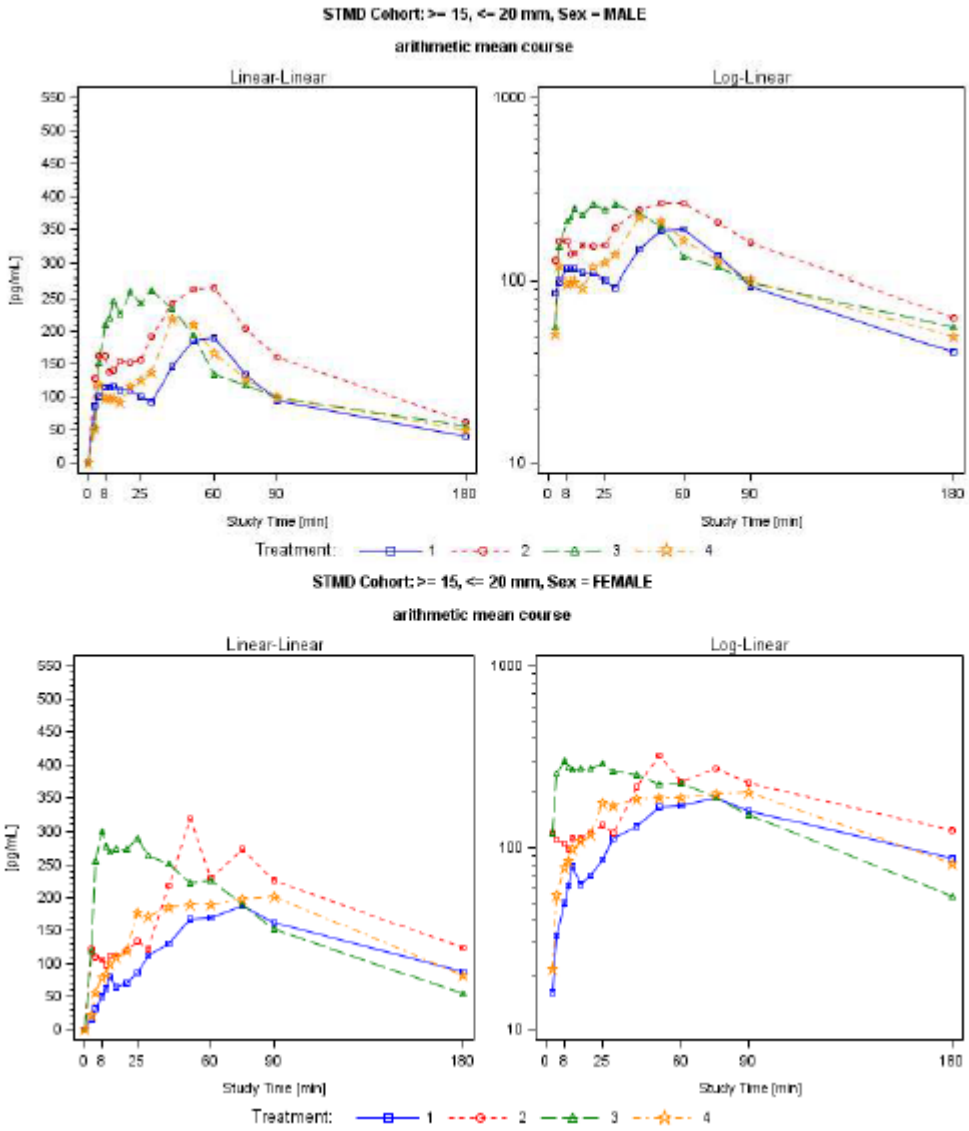


Figure 11. Mean plasma concentration time profiles of adrenaline up to 180 minutes, baseline corrected, Part 2, Cohort 1, by sex (pg/ml). STMD Cohort ≥ 15 mm, ≤ 20 mm, male (upper panel), female (lower panel).



Summary statistics of baseline corrected PK parameters are given in Table 1 and Table 2. AUC0-last and Cmax was compared between treatments. The Emerade 300/"Product 4" and Emerade 300/"Product 5" geometric LMS ratios for AUC0-last were 83.9% (90% CI: 76.31% to 92.32%) and 92.2% (90% CI: 83.88% to 101.38%). Geometric mean AUC0-last of baseline corrected epinephrine after Emerade 500 (31945 min*pg/mL) was about 1.3-fold to 1.6-fold higher compared to Emerade 300. The Emerade 300/"Product 4" and Emerade 300/"Product 5" geometric LSM ratios for Cmax were 66.6% (90% CI: 57.80% to 76.67%) and 93.7% (90% CI: 81.42-107.87%).

Table 1. Summary of the main PK parameters for baseline corrected adrenaline, by STMD cohort, Part 2.

		IMP 2 Emerade® 300 µg	IMP 3 Emerade® 500 µg	IMP 4 300 µg	IMP 5 300 µg
All Cohorts	**N**	**35***	**35***	**37**	**37**
$AUC_{0\text{-last}}$ (min*pg/mL)	Geom. mean	20528	31945	24649	22186
	Geom. CV%	51.6	42.3	32.8	43.7
$AUC_{0\text{-}5}$ (min*pg/mL)	Geom. mean	161.74	262.97	260.15	155.20
	Geom. CV%	164.4	186.3	186.0	226.5
$AUC_{0\text{-}10}$ (min*pg/mL)	Geom. mean	532.28	774.33	1102.0	597.08
	Geom. CV%	120.0	145.1	112.5	146.1
$AUC_{0\text{-}50}$ (min*pg/mL)	Geom. mean	5378	8508	10359	6478
	Geom. CV%	65.8	69.2	35.0	70.4
C_{max} (pg/mL)	Geom. mean	252.4	371.5	385.8	266.4
	Geom. CV%	63.5	58.2	41.3	63.0
t_{max} (min)	Median	60.0	50.0	25.0	40.0
	Min-Max	3.00-90.0	3.00-90.0	3.00-90.0	5.00-90.0
Cohort 1	**N**	**15**	**15**	**15**	**15**
$AUC_{0\text{-last}}$ (min*pg/mL)	Geom. mean	21242	29874	22033	22199
	Geom. CV%	51.9	43.7	33.2	44.9
$AUC_{0\text{-}5}$ (min*pg/mL)	Geom. mean	208.22	301.38	315.29	251.83
	Geom. CV%	228.0	222.6	304.8	192.2
$AUC_{0\text{-}10}$ (min*pg/mL)	Geom. mean	664.08	816.17	1180.3	873.43
	Geom. CV%	155.1	163.4	151.0	135.7
$AUC_{0\text{-}50}$ (min*pg/mL)	Geom. mean	6064	8538	9874	7515
	Geom. CV%	70.9	84.1	33.9	70.0
C_{max} (pg/mL)	Geom. mean	298.5	356.0	414.7	307.6
	Geom. CV%	77.8	72.2	49.8	81.4
t_{max} (min)	Median	50.0	50.0	20.0	40.0
	Min-Max	3.00-75.0	3.00-75.0	3.00-60.0	5.00-75.0
Cohort 2	**N**	**14***	**15**	**15**	**15**
$AUC_{0\text{-last}}$ (min*pg/mL)	Geom. mean	19797	29215	25012	21417
	Geom. CV%	47.4	34.2	29.9	45.4
$AUC_{0\text{-}5}$ (min*pg/mL)	Geom. mean	133.34	247.91	231.74	99.816
	Geom. CV%	152.4	207.2	166.0	220.4
$AUC_{0\text{-}10}$ (min*pg/mL)	Geom. mean	466.82	723.44	1166.0	436.78
	Geom. CV%	106.7	165.5	101.3	138.1
$AUC_{0\text{-}50}$ (min*pg/mL)	Geom. mean	4967	7620	11160	6032
	Geom. CV%	58.2	56.9	27.0	61.9
C_{max} (pg/mL)	Geom. mean	220.2	341.5	369.0	226.7
	Geom. CV%	46.7	45.5	35.5	51.4
t_{max} (min)	Median	60.0	50.0	20.0	50.0
	Min-Max	10.0-90.0	3.00-75.0	5.00-60.0	25.0-90.0
Cohort 3	**N**	**6**	**5***	**7**	**7**
$AUC_{0\text{-last}}$ (min*pg/mL)	Geom. mean	20507	51065	30383	23896
	Geom. CV%	70.6	28.3	30.0	43.4
$AUC_{0\text{-}5}$ (min*pg/mL)	Geom. mean	134.98	208.51	220.79	141.66
	Geom. CV%	63.5	80.9	57.4	262.2
$AUC_{0\text{-}10}$ (min*pg/mL)	Geom. mean	415.83	810.83	842.86	516.37
	Geom. CV%	69.5	73.8	68.6	163.3
$AUC_{0\text{-}50}$ (min*pg/mL)	Geom. mean	4797	11711	9787	5489
	Geom. CV%	77.5	59.0	53.5	93.3
C_{max} (pg/mL)	Geom. mean	228.2	543.4	363.3	276.3
	Geom. CV%	60.8	38.8	37.3	40.9
t_{max} (min)	Median	45.0	60.0	40.0	50.0
	Min-Max	10.0-90.0	40.0-90.0	25.0-90.0	5.00-90.0

N: number of subjects. Source: Table 14.2.3.1.2.2, Table 14.2.3.1.2.2a.

*Missing observations for Subjects 210 and 305 of were not included into the in the summary statistics and ANOVA on PK parameters

Table 2. Summary of the main PK parameters for baseline corrected adrenaline, Cohorts 1 and 2, by sex, Part 2.

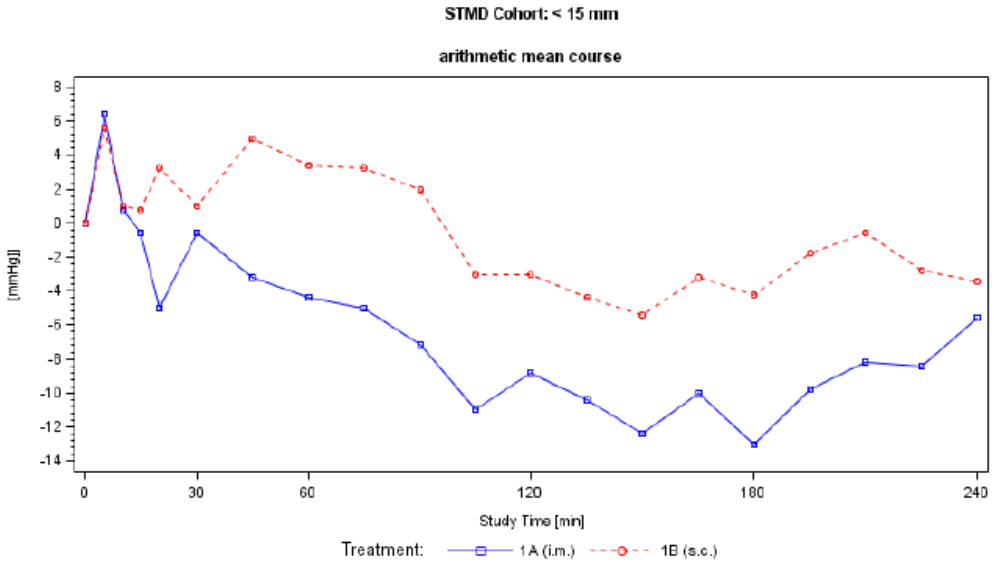
		IMP 2 Emerade® 300 µg		IMP 3 Emerade® 500 µg		IMP 4 300 µg		IMP 5 300 µg	
Cohort 1	**N**	**Male** 8	**Female** 7	**Male** 8	**Female** 7	**Male** 8	**Female** 7	**Male** 8	**Female** 7
$AUC_{0\text{-last}}$ (min*pg/mL)	Geom. mean	21738	20690	31118	28513	22726	21267	22479	21884
	Geom. CV%	65.7	38.1	59.7	21.8	38.4	29.0	53.6	37.7
$AUC_{0\text{-}5}$ (min*pg/mL)	Geom. mean	236.79	179.77	204.98	468.19	363.59	267.90	194.98	337.35
	Geom. CV%	144.5	413.2	367.9	92.4	502.3	195.2	160.4	243.5
$AUC_{0\text{-}10}$ (min*pg/mL)	Geom. mean	678.79	647.65	593.22	1175.3	1268.1	1087.3	702.55	1120.2
	Geom. CV%	111.1	241.1	232.8	88.0	173.5	145.5	132.0	144.2
$AUC_{0\text{-}50}$ (min*pg/mL)	Geom. mean	6171	5943	8214	8925	11129	8611	7157	7946
	Geom. CV%	66.4	83.0	123.1	42.8	33.1	30.9	98.1	38.5
C_{max} (pg/mL)	Geom. mean	281.7	318.9	386.0	324.6	444.4	383.2	287.7	332.0
	Geom. CV%	77.8	84.8	101.5	37.8	50.0	52.4	89.0	79.7
t_{max} (min)	Median	55.0	40.0	50.0	50.0	22.5	20.0	40.0	30.0
	Min-Max	5.0-60	3.0-75	3.0-75	3.0-60	3.0-50	3.0-60	30.0-60	5.0-75
Cohort 2	**N**	**Male** 7	**Female** 7	**Male** 8	**Female** 7	**Male** 8	**Female** 7	**Male** 8	**Female** 7
$AUC_{0\text{-last}}$ (min*pg/mL)	Geom. mean	18465	21225	26458	32720	22307	28507	18073	26002
	Geom. CV%	54.9	42.3	38.5	26.7	25.5	30.5	45.8	37.6
$AUC_{0\text{-}5}$ (min*pg/mL)	Geom. mean	293.42	60.597	404.78	141.56	201.85	271.35	169.98	54.321
	Geom. CV%	96.1	80.1	82.3	352.7	127.5	239.4	213.1	165.3
$AUC_{0\text{-}10}$ (min*pg/mL)	Geom. mean	811.38	268.58	1085.5	454.98	1075.1	1279.2	629.67	287.56
	Geom. CV%	95.3	57.7	76.3	263.4	73.9	143.8	99.5	164.0
$AUC_{0\text{-}50}$ (min*pg/mL)	Geom. mean	6030	4092	8007	7200	10551	11900	6384	5654
	Geom. CV%	55.8	56.1	71.6	42.4	21.1	33.3	48.5	80.6
C_{max} (pg/mL)	Geom. mean	226.6	213.9	297.3	400.1	333.2	414.7	213.3	243.2
	Geom. CV%	57.9	38.3	41.2	47.2	23.4	45.1	49.5	56.9
t_{max} (min)	Median	60.0	75.0	55.0	50.0	16.0	20.0	40.0	90.000
	Min-Max	10.0-60	40.0-90	40.0-75	3.0-75	5.0-40	5.017-60	40.0-60	25.0-90
Cohort 3	**N**	**Male** 0	**Female** 6	**Male** 0	**Female** 5	**Male** 0	**Female** 7	**Male** 0	**Female** 7
$AUC_{0\text{-last}}$ (min*pg/mL)	Geom. mean	n.a.	20507	n.a.	51065	n.a.	30383	n.a.	23896
	Geom. CV%	n.a.	70.6	n.a.	28.3	n.a.	30.0	n.a.	43.4
$AUC_{0\text{-}5}$ (min*pg/mL)	Geom. mean	n.a.	134.98	n.a.	208.51	n.a.	220.79	n.a.	141.66
	Geom. CV%	n.a.	63.5	n.a.	80.9	n.a.	57.4	n.a.	262.2
$AUC_{0\text{-}10}$ (min*pg/mL)	Geom. mean	n.a.	415.83	n.a.	810.83	n.a.	842.86	n.a.	516.37
	Geom. CV%	n.a.	69.5	n.a.	73.8	n.a.	68.6	n.a.	163.3
$AUC_{0\text{-}50}$ (min*pg/mL)	Geom. mean	n.a.	4797	n.a.	11711	n.a.	9787	n.a.	5489
	Geom. CV%	n.a.	77.5	n.a.	59.0	n.a.	53.5	n.a.	93.3
C_{max} (pg/mL)	Geom. mean	n.a.	228.2	n.a.	543.4	n.a.	363.3	n.a.	276.3
	Geom. CV%	n.a.	60.8	n.a.	38.8	n.a.	37.3	n.a.	40.9
t_{max} (min)	Median	n.a.	45.0	n.a.	60.0	n.a.	40.0	n.a.	50.0
	Min-Max	n.a.	10.0-90	n.a.	40.0-90	n.a.	25-90	n.a.	5.0-90

N: number of subjects. n.a.: not applicable. Source: Table 14.2.3.2.2.2, Table 14.2.3.2.2.2a

Pharmacodynamic results

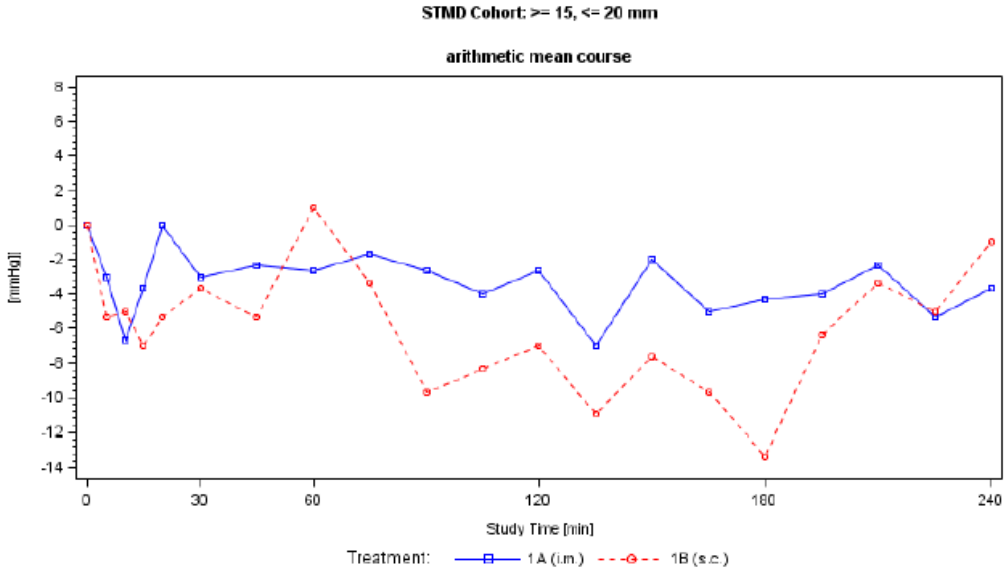
Part 1:
In Cohort 1 (STMD < 15 mm), the mean systolic blood pressure increased by 6.4 mm Hg within 5 minutes after i.m. administration and subsequently decreased to baseline levels within the first 15 minutes. Subsequently, the mean systolic blood pressure continued to decrease. A similar, but less pronounced course was observed after s.c. administration (Figure 12). In cohort 2 (≥ 15 mm to < 20 mm), the mean systolic blood pressure decreased within the first 10-20 minutes after both i.m. and s.c. administration (Figure 13).

Figure 12. Mean change from baseline in systolic blood pressure by treatment and STMD cohort, Part 1, Cohort 1. STMD < 15 mm.



Treatment 1A=Suprarenin 500 µg, i.m., Treatment 1B=Suprarenin 500 µg, s.c.
Source: Table 14.2.4.1.1.2, Figure 14.2.5.1.1.2.

Figure 13. Mean change from baseline in systolic blood pressure by treatment and STMD cohort, Part 1, Cohort 2. STMD ≥ 15, ≤ 20 mm.

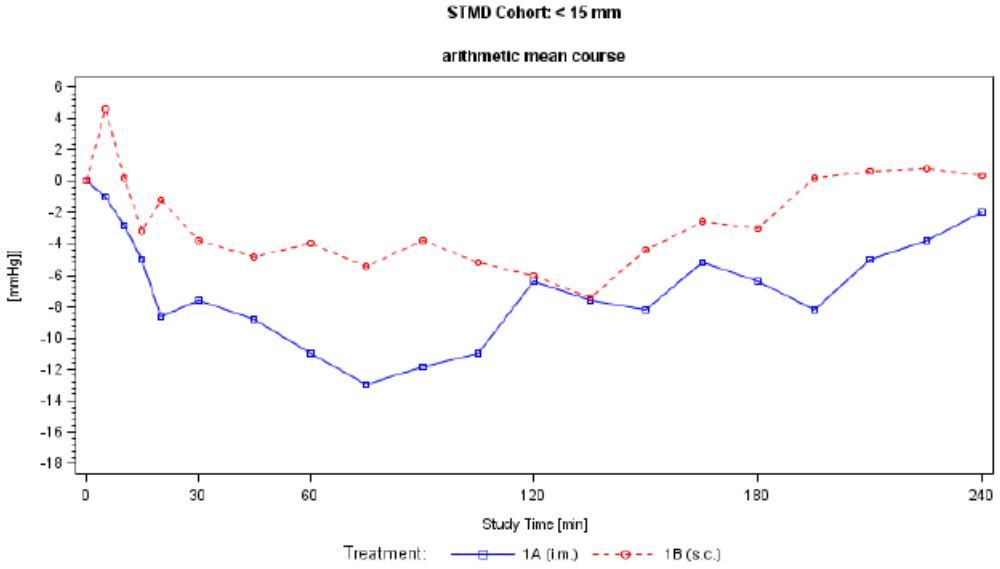


Treatment 1A= Suprarenin 500 µg, i.m., Treatment 1B= Suprarenin 500 µg, s.c.
Source: Table 14.2.4.1.1.2, Figure 14.2.5.1.1.2.

After i.m. administration of the IMP, the mean diastolic blood pressure immediately decreased, reaching a maximum descent of 12-13 mm Hg at 60-75 minutes after dosing in both Cohort 1 and Cohort 2. Afterwards, the mean diastolic blood pressure increased, returning to near baseline values at 4 hours post-dose. After s.c. administration of the IMP, the diastolic blood pressure initially increased by 4.6 mm Hg at 5 minutes (Cohort 1) or decreased (Cohort 2),

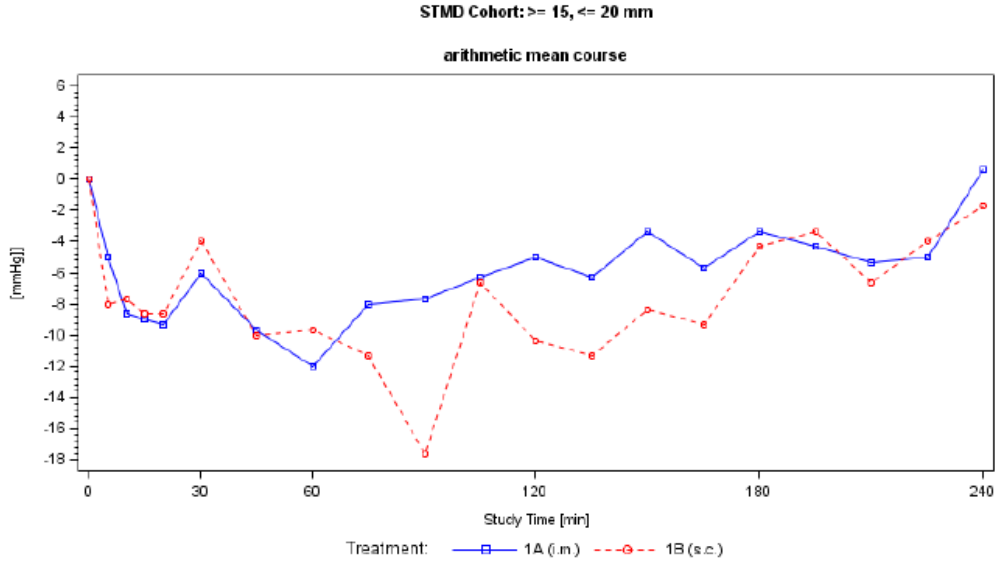
after which it decreased in a similar, but less pronounced manner to i.m. administration (Figure 14 and Figure 15).

Figure 14. Mean change from baseline in diastolic blood pressure by treatment and STMD cohort, Part 1, Cohort 1. STMD < 15 mm.



Treatment 1A= Suprarenin 500 µg, i.m., Treatment 1B= Suprarenin 500 µg , s.c.
Source: Table 14.2.4.1.1.2, Figure 14.2.5.1.1.3.

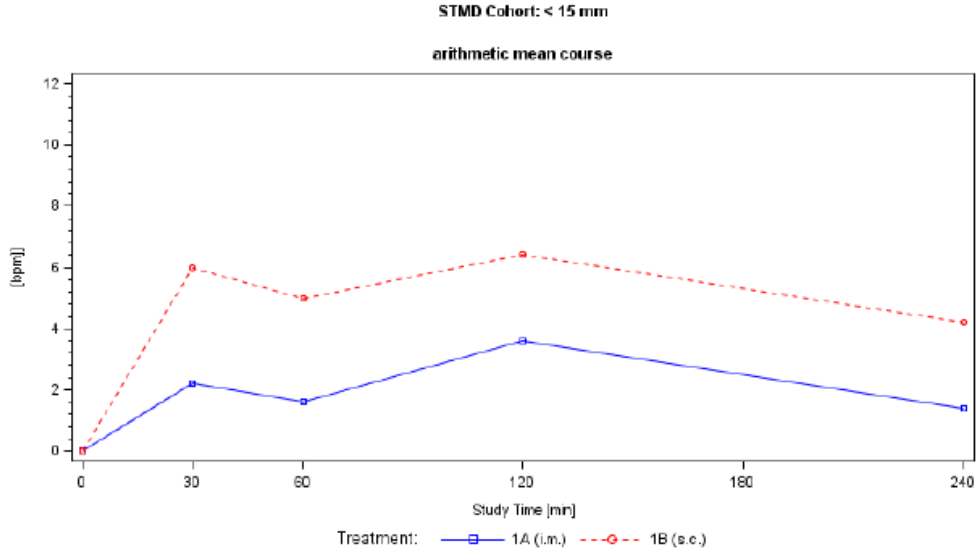
Figure 15. Mean change from baseline in systolic blood pressure by treatment and STMD cohort, Part 1, Cohort 2. STMD ≥ 15, ≤ 20 mm.



Treatment 1A= Suprarenin 500 µg, i.m., Treatment 1B= Suprarenin 500 µg, s.c.
Source: Table 14.2.4.1.1.2, Figure 14.2.5.1.1.3.

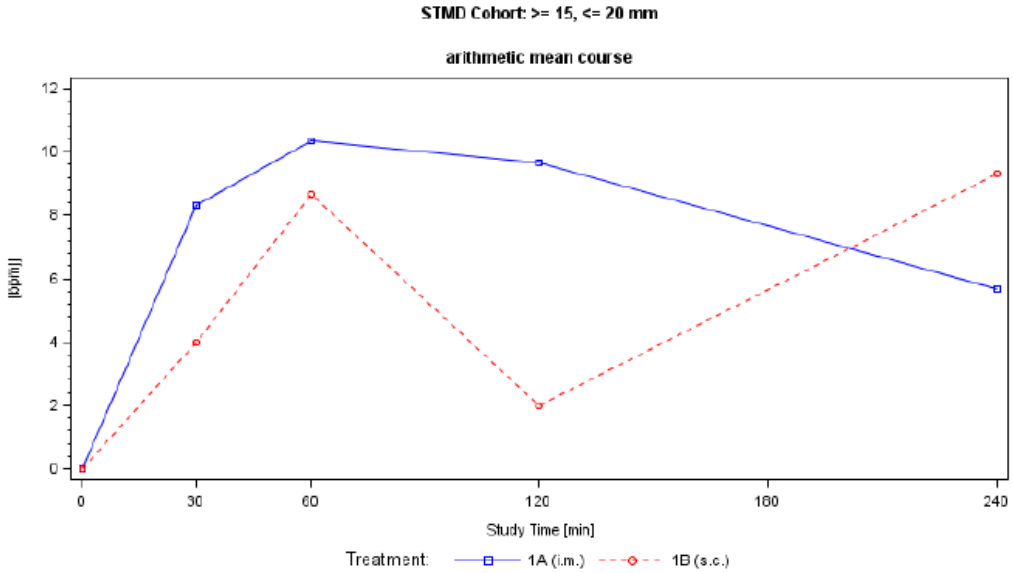
Mean changes from baseline in heart rate were marginal. A slight increase reaching a maximum mean increase of 3.6 bpm (Cohort 1) and 10.3 bpm (Cohort 2) in the i.m. group and 6.4 bpm (Cohort 1) and 8.7 bpm (Cohort 2) in the s.c. group was observed approximately 2 hours after drug administration (Figure 16 and Figure 17).

Figure 16. Mean change from baseline in heart rate by treatment and STMD cohort, Part 1, Cohort 1. STMD < 15 mm.



Treatment 1A= Suprarenin 500 µg, i.m., Treatment 1B= Suprarenin 500 µg, s.c.
Source: Table 14.2.4.1.1.2, Figure 14.2.5.1.1.1.

Figure 17. Mean change from baseline in heart rate by treatment and STMD cohort, Part 1, Cohort 2. STMD ≥ 15, ≤ 20 mm.



Treatment 1A= Suprarenin 500 µg, i.m., Treatment 1B= Suprarenin 500 µg, s.c.
Source: Table 14.2.4.1.1.2, Figure 14.2.5.1.1.1.

Part 2:

The results from Part 2, by Cohort, is presented in the figures below. Overall the results were similar as those observed in Part 1.

Figure 18. Mean change from baseline in systolic blood pressure by treatment and STMD cohort, Part 2, Cohort 1. STMD < 15 mm.

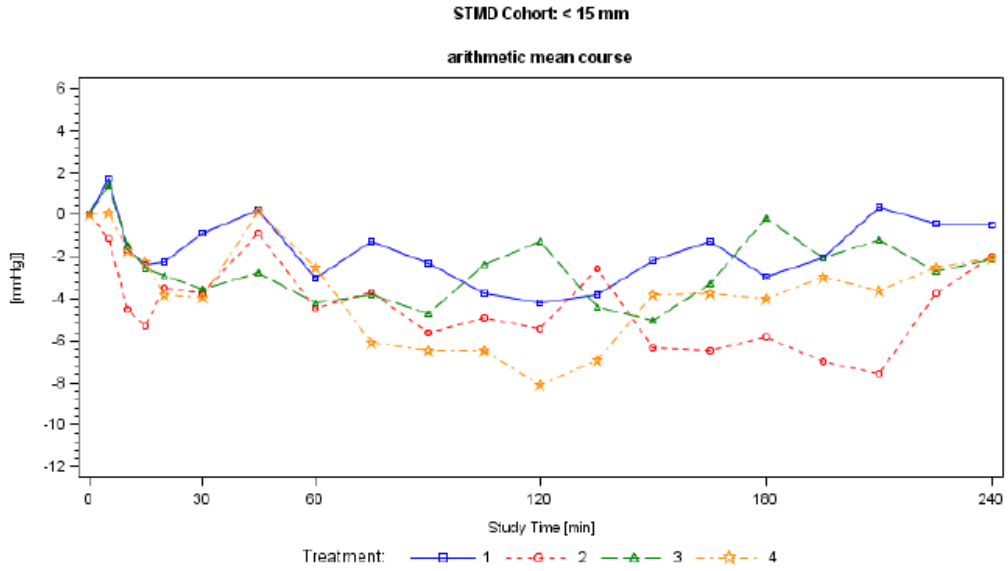


Figure 19. Mean change from baseline in diastolic blood pressure by treatment and STMD cohort, Part 2, Cohort 1. STMD < 15 mm.

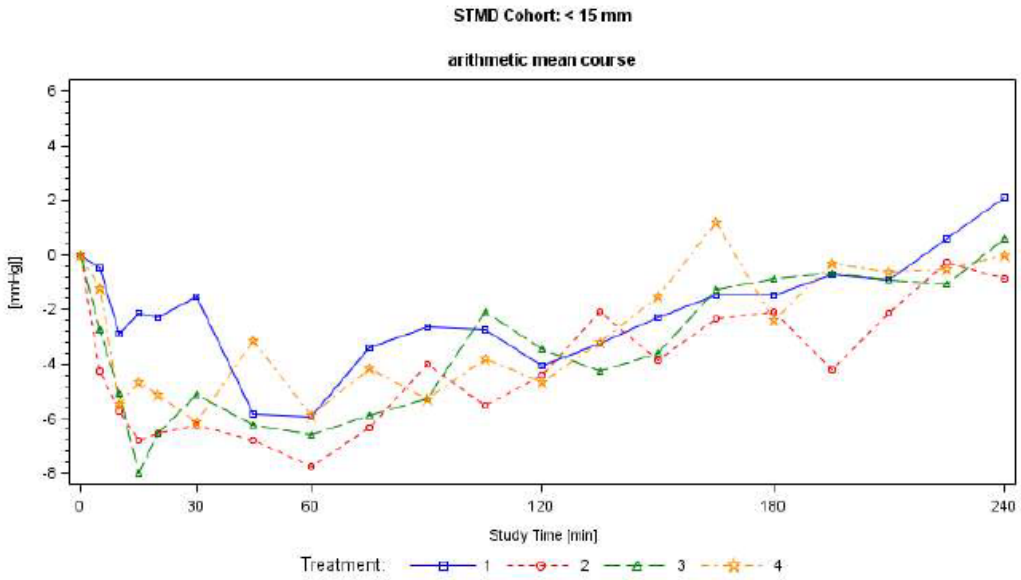


Figure 20. Mean change from baseline in heart rate by treatment and STMD cohort, Part 2, Cohort 1. STMD < 15 mm.

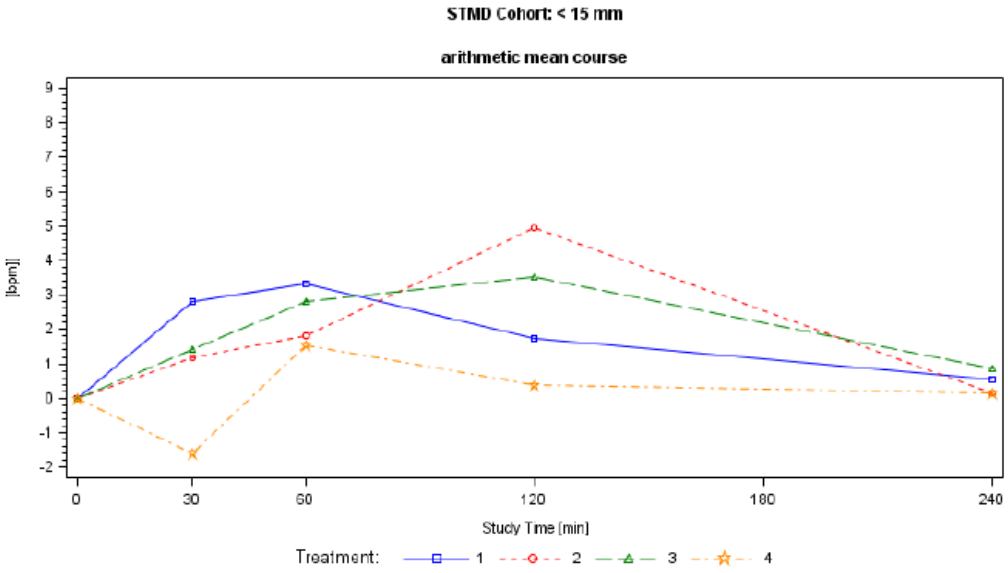


Figure 21. Mean change from baseline in systolic blood pressure by treatment and STMD cohort, Part 2, Cohort 2. STMD ≥ 15, ≤ 20 mm.

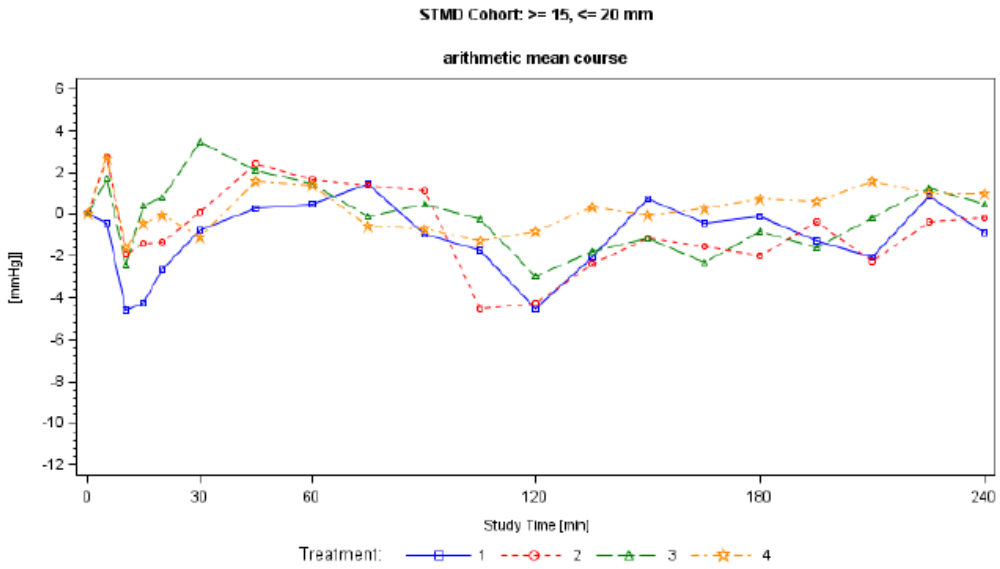


Figure 22. Mean change from baseline in diastolic blood pressure by treatment and STMD cohort, Part 2, Cohort 2. STMD ≥ 15, ≤ 20 mm.

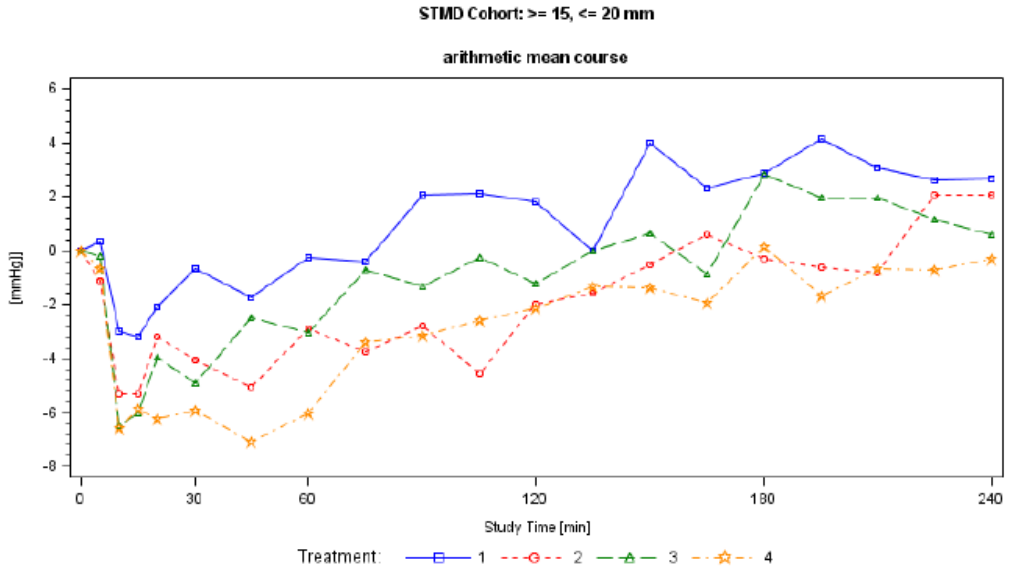


Figure 23. Mean change from baseline in heart rate by treatment and STMD cohort, Part 2, Cohort 2. STMD ≥ 15, ≤ 20 mm.

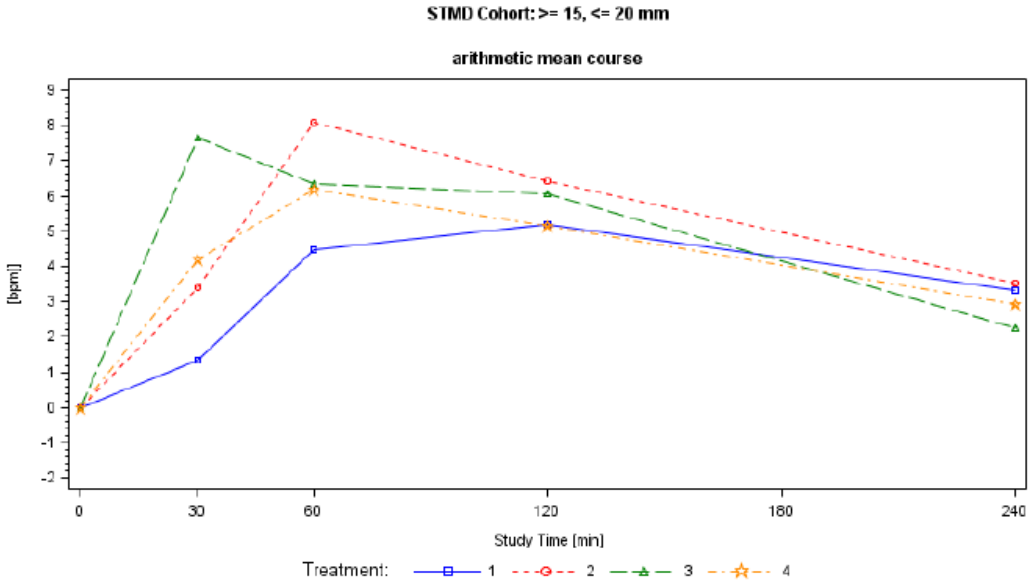


Figure 24. Mean change from baseline in systolic blood pressure by treatment and STMD cohort, Part 2, Cohort 3. STMD > 20 mm.

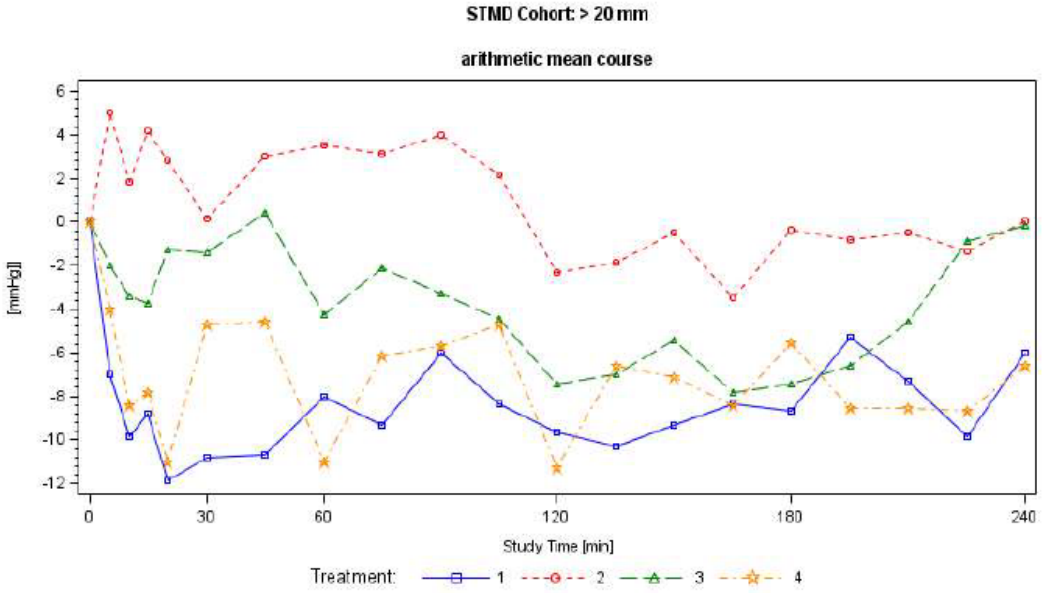


Figure 25. Mean change from baseline in diastolic blood pressure by treatment and STMD cohort, Part 2, Cohort 3. STMD > 20 mm.

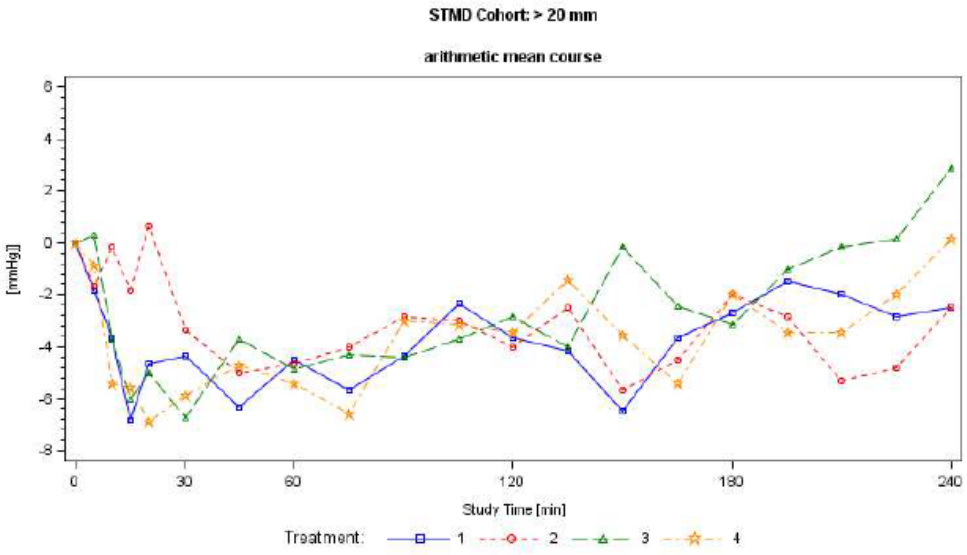
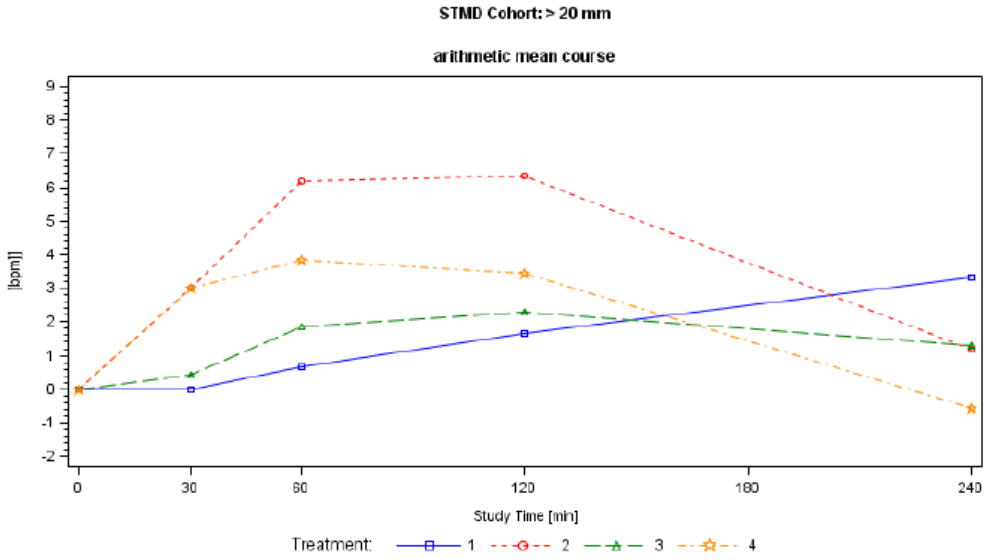


Figure 26. Mean change from baseline in heart rate by treatment and STMD cohort, Part 2, Cohort 3. STMD > 20 mm.



Overall conclusion and benefit/risk assessment

The pharmacokinetic results are variable but indicate that the absorption is slower in subjects with large STMD, which may result in a slower onset of effect or an inadequate response. The pharmacodynamic results was not conclusive and hence, the study does unfortunately not provide further information on the exposure response relationship. It is therefore not possible to predict whether therapeutic plasma concentrations have been reached in this sub-population or not. As a precautionary measure, additional information has been added in section 4.4 and section 5.2 of the SmPC; *In patients with thick sub-cutaneous fat layer, there is a risk of adrenaline being administered in the sub-cutaneous tissue which may result in a slower adrenaline absorption and a suboptimal effect. This may increase the need for a second Emerade injection. This underlines the importance of carrying two Emerade devices at all times.*

The products, Emerade, 300 microgram and 500 microgram, solution for injection in pre-filled pen, were approved previously and the benefit/risk for the products remains unchanged.