2 Synopsis

Name of Sponsor/Company: ALK-Abelló A/S	**Individual Trial Table Referring to Part of the Dossier**	**(For National Authority Use Only)**
Name of Finished Product: Jext® adrenaline autoinjector	**Volume:**	
Name of Active Ingredients: adrenaline	**Page:**	
Title of trial:	Open-label trial investigating the pharmacokinetic profile of adrenaline obtained following administration by the Jext® autoinjector and by manual intramuscular injection in subjects with varying skin to muscle depths	
Trial numbers:	[redacted] Trial Number: 228695 Sponsor Trial ID: JX-A-03	
Investigational medicinal product:	Jext® adrenaline autoinjector	
Development phase:	Phase 1	
Sponsor:	ALK-Abelló A/S Bøge Alle 6-8 DK 2970 Hørsholm Denmark	
Principal investigator:	Dr [redacted]	
Trial centre:	[redacted] Early Phase Clinical Unit (EPCU) – Berlin, [redacted] Berlin, Germany	
Publication:	None	
Trial duration:	First subject screened: 17 January 2017 Last subject completed: 18 April 2017	

Trial objectives:

Primary objective:

The primary objective of the trial was to assess the pharmacokinetic (PK) properties (C_{max} and t_{max}) of 0.3 mg of adrenaline administered via the Jext® autoinjector compared to 0.3 mg adrenaline administered via intramuscular (IM) injection by syringe, based on ultrasound measurements in adult volunteers with varying skin to muscle depth (STMD).

Secondary objectives:

The secondary objectives of the trial were:

- To compare the PK properties $t_{½}$, $AUC_{0-\infty}$, AUC_{0-t} (t = 4, 8, 16 and 30 minutes, 1 hour and last measurable concentration) and the absorbtion constant (k_a) obtained after administration of 0.3 mg of adrenaline administered using Jext® autoinjector and 0.3 mg adrenaline administered by manual IM injection by syringe, based on ultrasound measurements in adult volunteers with varying STMDs
- To compare the pharmacodynamics (PD) effect on systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate of adrenaline delivered by Jext® and IM injection by syringe
- To assess safety and tolerability of 0.3 mg adrenaline delivered by Jext®
- To investigate the relationship between STMD and the following parameters: body mass index (BMI), weight, thigh circumference and thigh fat caliper measurements

Exploratory objectives:

The exploratory objectives of the trial were:

- To investigate the relationship between STMD and PK parameters
- To investigate the relationship between mid-thigh STMD and distal-thigh STMD
- To investigate the relationship between PK and PD

Trial design:

The trial was a phase 1, single-site, non-therapeutic, randomised, open-label, 2-treatment, 4-sequence cross-over trial

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to evaluate the PK profile obtained following administration of 0.3 mg adrenaline administered via Jext® autoinjector and 0.3 mg adrenaline administered via IM injection by manual syringe based on ultrasound measurements in subjects with varying STMDs.

Methodology:

A total of 24 subjects were randomised to receive 4 treatments in random sequence. The STMD at the distal and mid-thigh of both thighs were measured with compression by ultrasound at screening. Subjects were included into 3 cohorts of 8 subjects each, depending on the compressed mid-thigh STMD (average of the left and right thigh measurements), as follows:

- Cohort 1: STMD < 15 mm
- Cohort 2: STMD ≥ 15 mm and ≤ 20 mm
- Cohort 3: STMD > 20 mm

Trial subjects:

Planned for inclusion:	24 subjects
Enrolled and randomised:	24 subjects
Withdrawn:	One subject [redacted] was withdrawn prematurely; the subject received 1 dose of investigational medicinal product (IMP), i.e., 1 dose of 0.3 mg adrenaline via Jext® autoinjector, before being withdrawn from the trial
Excluded from analysis:	Subject [redacted] was excluded from the PK and PD analysis sets
Analysed:	Safety population: 24 subjects PK analysis set: 23 subjects PD analysis set: 23 subjects

Diagnosis and main criteria for inclusion:

To be eligible to participate in this trial, all of the following main criteria had to be met:

- Written informed consent obtained before any trial related procedures were performed.
- Male and female volunteers ≥ 18 and ≤ 45 years of age (at screening).
- A female subject of childbearing potential had to have a negative pregnancy test and both male and female subjects had to be willing to practice appropriate contraceptive methods with a failure rate of < 1% until the follow up visit. Male subjects had to refrain from sperm donation from Day -1 until at least 1 month after the last dose.
- Subjects with a mid-thigh compressed STMD < 15 mm, STMD ≥ 15 mm and ≤ 20 mm or STMD > 20 mm.
- Subjects with BMI of 20-40 kg/m_2.
- Subjects had to be non-smokers; previous smokers should have quit more than 2 years ago and the pack year had to be ≤ 5.
- Subjects with no clinically significant abnormal serum biochemistry, haematology (including coagulation parameters international normalised ratio [INR], prothrombin time [PT] and activated partial thromboplastin time [aPTT]) and urine examination values at screening and Day -1.
- Subjects with potassium ≥ 3 mmol/L and not > the upper limit of normal (ULN).
- Subjects with a negative urinary drugs of abuse screen, determined at screening and Day -1.
- Subjects with negative human immunodeficiency virus (HIV) and Hepatitis B and C results.
- Subjects with suitable veins for insertion of a peripheral venous catheter.
- Subjects with no clinically significant abnormalities in 12-lead electrocardiogram (ECG) determined at screening and prior to each dose; corrected QT interval calculated using Fridericia's formula (QTcF) should have been ≤ 500 msec.
- No clinically significant abnormalities in 12-lead ECG during a cardiac stress test at screening.
- No significant structural abnormalities in echocardiogram examination at screening.
- Subjects with no clinically significant deviation outside the normal ranges for blood pressure (90-140 mmHg for

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SBP and 50-90 mmHg for DBP) and heart rate (45-90 beats per minute [bpm]) measured in supine position.

- Subjects had to be available to complete the trial.
- Subjects had to satisfy a medical examiner about their fitness to participate in the trial.
- Subjects had to be willing and able to comply with the trial protocol.

Protocol deviations:

There were 6 deviations related to missing/delayed collection of blood samples related to the PK analysis for the trial, that were classified as major (these involved Subject [redacted] . The samples with major deviations due to time delay were not used in the summary tables, but they were used in the non-compartmental analysis. All other protocol deviations were classified as minor. None of the reported deviations from the protocol required that any subject be excluded from the analysis sets or had an effect on the interpretation of the trial results.

Investigational products, dose and mode of administration, batch numbers:

Active treatment:

Active ingredients:	Adrenaline-tartrate
Dosage form:	IM via Jext® autoinjector
Dose/strength:	0.3 mg / 0.3 mL / 1 mg/mL
Batch number:	R4055
Expiry date:	December 2017

Comparator treatment:

Active ingredients:	Adrenaline hydrogentartrate
Dosage form:	IM via syringe
Dose/strength:	0.3 mg / 0.3 mL / 1 mg/mL
Batch number:	M051606
Expiry date:	May 2018

Duration of treatment:

Each subject received 4 doses of 0.3 mg adrenaline in this trial, i.e., 2 doses administered via Jext® autoinjector and 2 doses administered via IM injection by syringe based on ultrasound measurements.

The intervals between doses were at least 24 hours. The trial was a fully replicated design with the test product (Jext® autoinjector, J) and the reference product (IM injection by syringe, IM) administered twice in a random sequence (J-IM-IM-J; IM-J-J-IM; J-J-IM-IM; IM-IM-J-J).

Criteria for evaluation:

Primary endpoint:

Primary endpoint:

- The derived PK parameters C_{max} and t_{max} after IM injection and Jext® injection.

Baseline corrected plasma concentrations were used for the primary endpoint.

Secondary endpoints:

Secondary endpoints:

- The PK parameters $t_{½}$, $AUC_{0-\infty}$, AUC_{0-t} (t = 4, 8, 16 and 30 minutes, 1 hour and last measurable concentration) and k_a after IM injection and Jext® injection
- Time to maximum effect on PD parameters (SBP, DBP, heart rate)
- STMD related to BMI, weight, thigh circumference and thigh fat caliper measurements

Safety endpoints:

- Treatment emergent adverse events (TEAEs)

Exploratory endpoints:

Exploratory endpoints:

- STMD related to PK parameters
- Mid-thigh STMD and distal-thigh STMD

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- PK parameters (C_{max}, t_{max} and AUC) and PD parameters (E_{max} and AUEC)

Statistical methods:

Plasma adrenaline concentrations (absolute and baseline corrected) and PK parameters were listed by subject and summarised appropriately by means of descriptive statistics and/or graphically. The log-transformed PK parameter C_{max} of baseline corrected concentrations was compared between treatments using an analysis of variance (ANOVA) model (with treatment, cohort and the interaction between treatment and cohort as fixed factors). In addition the treatment effect was estimated for each cohort. Between subject variability and residual error were estimated for each cohort. The PK parameter t_{max} was analysed using the Mack-Skillings approach. Only subjects who had t_{max} values for all periods were included in the analysis. The statistic was evaluated using the chi-squared distribution.

The PD parameters (blood pressure and heart rate) were listed by subject and summarised by treatment descriptively. The PD parameters (E_{max}, t_{max} and AUEC) of baseline corrected blood pressure and heart rate were to be compared between treatments using an ANOVA model. This comparison could, however, not be performed for the observed data.

The PK/PD relationships between C_{max} and AUC_{0-t} of adrenaline and PD endpoints (E_{max} and AUEC for all PD variables) were explored. Preliminary exploratory graphically analyses were done to assess the shape of the potential relationship between PK and PD endpoints.

The STMDs were listed by subject, visit and location. Descriptive statistics were presented by time point and location. The same analysis was presented by STMD cohort.

Summary statistics of PK parameters ($t_{½}$ and baseline corrected C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, AUC_{0-4}, AUC_{0-8}, AUC_{0-16}, AUC_{0-30}) were presented by STMD cohorts and treatment.

Results for BMI, weight, thigh circumference and mid-thigh fat caliper were listed by subject. Summary statistics of BMI, weight, thigh circumference were provided by STMD cohort.

Results from safety assessments were listed by subject and summarised appropriately by means of descriptive statistics.

Summary – results:

Pharmacokinetic and pharmacodynamics results:

- Adrenaline mean concentrations increased rapidly within the first 4 to 8 minutes (first apparent peak) following administration of 0.3 mg via Jext® autoinjector and IM syringe followed by a slower increase (second apparent peak) to reach maximum at 40 and 30 minutes, respectively. When presented by STMD cohort, the same pattern of absorption was observed; maximum concentrations were reached at approximately 30 minutes (t_{max} ranged from 4 to 90 minutes) with the exception of Jext® autoinjector for the ≥ 15 to ≤ 20 mm STMD cohort that had an earlier t_{max} (median 12 minutes with range from 4 to 90 minutes) and Jext® autoinjector for the > 20 mm STMD cohort that had a later t_{max} (median 60 minutes with range from 8 to 120 minutes).
- There was no statistically significant difference in t_{max} between the Jext® autoinjector and IM syringe.
- Geometric mean C_{max} values were comparable for the Jext® autoinjector and IM syringe treatments overall and by STMD cohort. Equivalence between the Jext® autoinjector and IM syringe treatments was observed for C_{max} based on geometric mean ratios close to 1, while confidence limits were wide for the analysis by STMD cohort, indicating that caution should be taken when interpreting these data.
- Total exposure (AUC_{0-t} and AUC_{0-inf}) was slightly higher (overall ratios 1.33 and 1.28, respectively) for the Jext® autoinjector compared to the IM syringe. This overall difference, which seemed significant based on evaluation of the treatment ratios and the corresponding CIs, was slightly lower for the < 15 mm STMD cohort (with the exception of AUC_{0-inf}), not observed for the intermediate STMD cohort, and more pronounced for the > 20 mm STMD cohort (ratios 1.92 and 1.66, respectively).
- The exposure within the first 60 minutes after dose was variable but overall comparable for the Jext® autoinjector and IM syringe treatments, suggesting equivalence. When presented by STMD cohort, even though comparable between treatments, AUC_{0-60} tends to be lower with increasing skin depth.
- The partial AUC values within the first 30 minutes after doses were comparable for Jext® autoinjector and IM syringe treatments overall, with a tendency towards lower exposure for the Jext® autoinjector treatment. When presented by STMD cohort, the lower exposure within the first 30 minutes for the Jext® autoinjector compared with IM syringe was more pronounced in the > 20 mm STMD cohort for which ratios ranged between 0.27 for the

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AUC_{0-4} to 0.66 for the AUC_{0-30}, while the < 15 mm and ≥ 15 and ≤ 20 mm cohorts produced slightly higher exposures for the Jext® autoinjector compared with IM syringe.

- The elimination half-life was approximately 30 to 40 minutes and slightly but consistently longer for the Jext® autoinjector compared to IM syringe treatments overall and by STMD cohort.
- The results suggest that adrenaline administration in the various STMD cohorts produce similar results with respect to t_{max} and C_{max} and that overall results are comparable between the Jext® autoinjector and IM syringe treatments. Overall exposure in terms of AUC were also comparable between treatments; however, in the > 20 mm STMD cohort, the Jext® autoinjector treatment seems to have a slightly slower but persistent absorption compared to the IM syringe treatment and the 2 other cohorts. This is observed by a lower AUC in the first 30 minutes but higher overall AUC.
- For the Jext® autoinjector the various STMD cohorts showed similar results with regards to mean $t_{½}$. For IM syringe injection, mean $t_{½}$ values vary between the STMD cohorts. Overall, mean $t_{½}$ for Jext® autoinjector is longer than for IM syringe injection.
- Results for mean vital signs measurements were comparable for the Jext® autoinjector and IM syringe treatments.
- Graphical analysis of E_{max} and AUEC for diastolic and systolic blood pressure and heart rate compared with plasma C_{max} and AUC_{0-t} showed no clear trend for any relationship between the endpoints.

Safety results:

In this trial, the number and type of TEAEs were similar between the Jext® autoinjector and IM injection treatment groups. The majority of TEAEs were assessed to be of mild intensity. There were no SAEs assessed as related to the IMP.

There were no treatment related or clinically relevant trends for any of the safety laboratory parameters, vital signs measurements, 12-lead ECG parameters or results from physical examinations performed during the trial.

Overall, single doses of adrenaline administered by Jext® autoinjector and IM injection by syringe were well tolerated by healthy subjects in this trial and no new safety signals were observed.

Overall conclusion:

In summary, the results suggest that adrenaline administration in subjects with varying STMD produce similar results with respect to t_{max}, C_{max} and AUC when administered by Jext® autoinjector or IM syringe, and that overall results are comparable between the 2 treatments. The Jext® autoinjector treatment in the > 20 mm STMD cohort seems to have a slightly slower but persistent absorption, compared to the IM syringe treatment and the 2 other cohorts. This leads to lower AUC in the first 30 minutes but higher overall AUC with a slightly longer $t_{½}$, due to the persistent absorption. No new safety signals were observed.

Date of report: Final 1.0, 30 October 2017

This trial was conducted in compliance with International Council for Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki.