Val av adrenalinpenna

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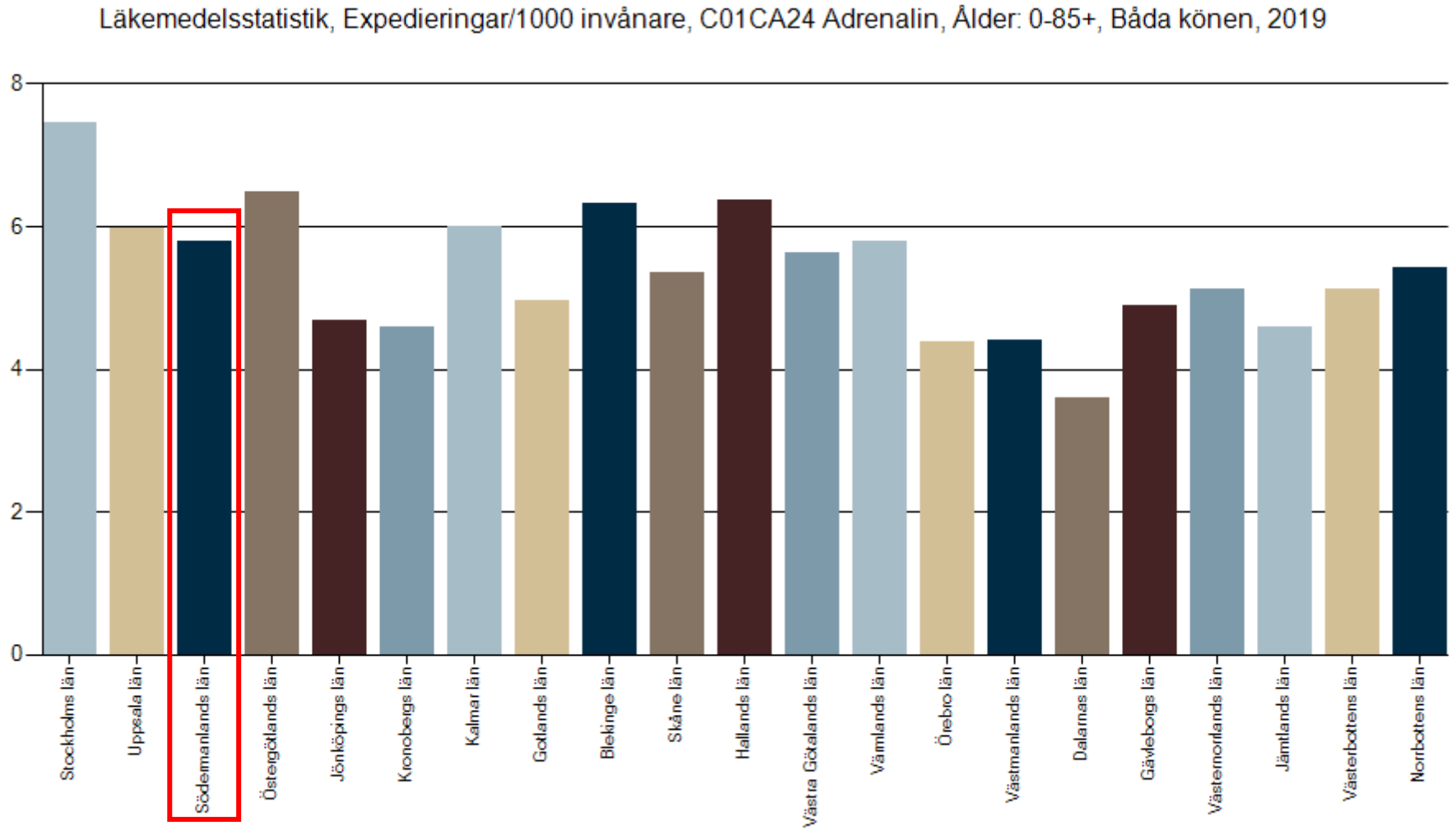
Region Sörmland och Karolinska Institutet

Uppdrag för Mylan:
Global Digital Advisory Board
Meeting Febr 2021

Förskrivning av adrenalinpennor i Sörmland, 2019



1709 expedieringar 95% kasseras

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Med tanke på att så många förskrivna pennor inte används/kasseras samtidigt som anafylaxi är ett potentiellt livshotande tillstånd:

- Är diagnosen korrekt?
- Vet patienten när det är dags att injicera?
- Kan patienten injicera
- Bär patienten sprutorna på sig
- Har patienten fått en tvåpack med adrenalinpennor förskrivet

Se SFFA.nu /dokument/anafylaxidokumentet

Spelar val av adrenalinpenna någon roll?

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Vilka faktorer kan vara av betydelse för en optimal och effektiv serumkoncentration

- Dos (0,15 mg; 15-30 kg, 0,30 mg; 30-60 kg, 0,50 mg; >60 kg?)
- Nållängd
- Injektionskraft
- Hållbarhet

- Enkelhet för att optimera korrekt injektion
- Förvaring

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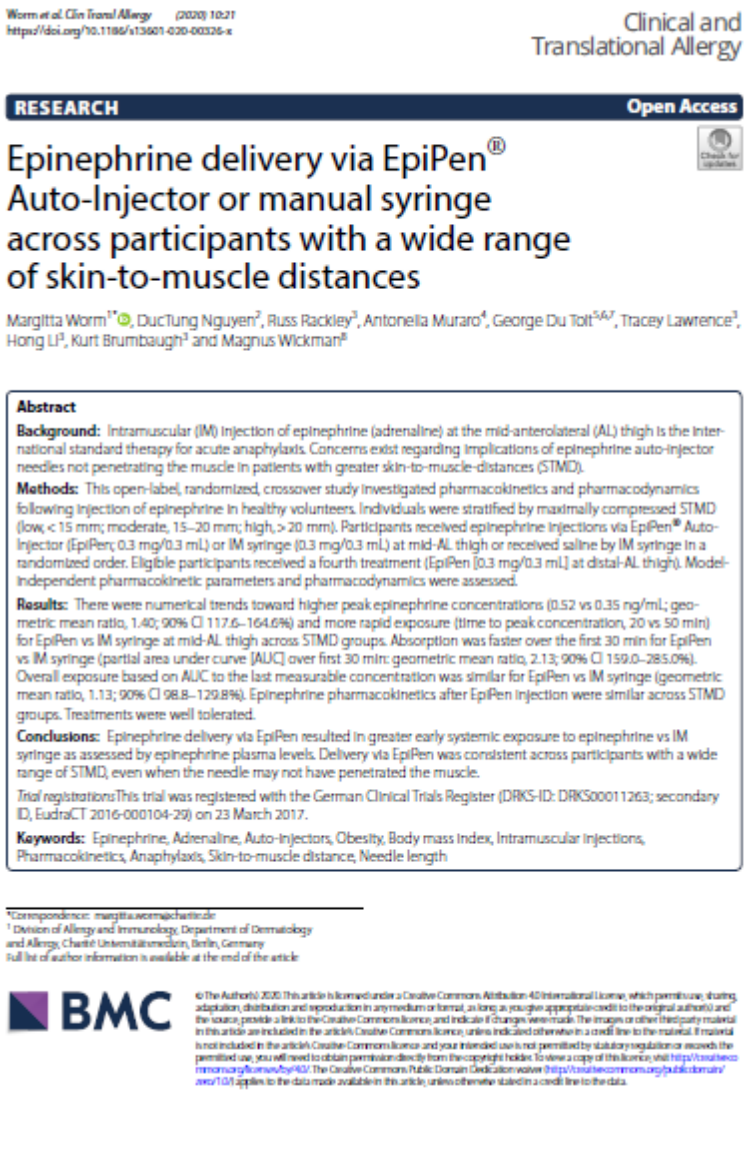
Studier initierade av EMA 2016



Worm et al. Clin Transl Allergy (2020) 10:21
https://doi.org/10.1186/s13601-020-00326-x

Clinical and Translational Allergy

RESEARCH Open Access

Epinephrine delivery via EpiPen® Auto-Injector or manual syringe across participants with a wide range of skin-to-muscle distances

Margitta Worm[1*], DucTung Nguyen[2], Russ Rackley[3], Antonella Muraro[4], George Du Toit[5,6,7], Tracey Lawrence[3], Hong Li[3], Kurt Brumbaugh[3] and Magnus Wickman[8]

Abstract

Background: Intramuscular (IM) injection of epinephrine (adrenaline) at the mid-anterolateral (AL) thigh is the international standard therapy for acute anaphylaxis. Concerns exist regarding implications of epinephrine auto-injector needles not penetrating the muscle in patients with greater skin-to-muscle-distances (STMD).

Methods: This open-label, randomized, crossover study investigated pharmacokinetics and pharmacodynamics following injection of epinephrine in healthy volunteers. Individuals were stratified by maximally compressed STMD (low, < 15 mm; moderate, 15–20 mm; high, > 20 mm). Participants received epinephrine injections via EpiPen® Auto-Injector (EpiPen; 0.3 mg/0.3 mL) or IM syringe (0.3 mg/0.3 mL) at mid-AL thigh or received saline by IM syringe in a randomized order. Eligible participants received a fourth treatment (EpiPen [0.3 mg/0.3 mL] at distal-AL thigh). Model-independent pharmacokinetic parameters and pharmacodynamics were assessed.

Results: There were numerical trends toward higher peak epinephrine concentrations (0.52 vs 0.35 ng/mL; geometric mean ratio, 1.40; 90% CI 117.6–164.6%) and more rapid exposure (time to peak concentration, 20 vs 50 min) for EpiPen vs IM syringe at mid-AL thigh across STMD groups. Absorption was faster over the first 30 min for EpiPen vs IM syringe (partial area under curve [AUC] over first 30 min: geometric mean ratio, 2.13; 90% CI 159.0–285.0%). Overall exposure based on AUC to the last measurable concentration was similar for EpiPen vs IM syringe (geometric mean ratio, 1.13; 90% CI 98.8–129.8%). Epinephrine pharmacokinetics after EpiPen injection were similar across STMD groups. Treatments were well tolerated.

Conclusions: Epinephrine delivery via EpiPen resulted in greater early systemic exposure to epinephrine vs IM syringe as assessed by epinephrine plasma levels. Delivery via EpiPen was consistent across participants with a wide range of STMD, even when the needle may not have penetrated the muscle.

Trial registrations This trial was registered with the German Clinical Trials Register (DRKS-ID: DRKS00011263; secondary ID, EudraCT 2016-000104-29) on 23 March 2017.

Keywords: Epinephrine, Adrenaline, Auto-Injectors, Obesity, Body mass Index, Intramuscular Injections, Pharmacokinetics, Anaphylaxis, Skin-to-muscle distance, Needle length

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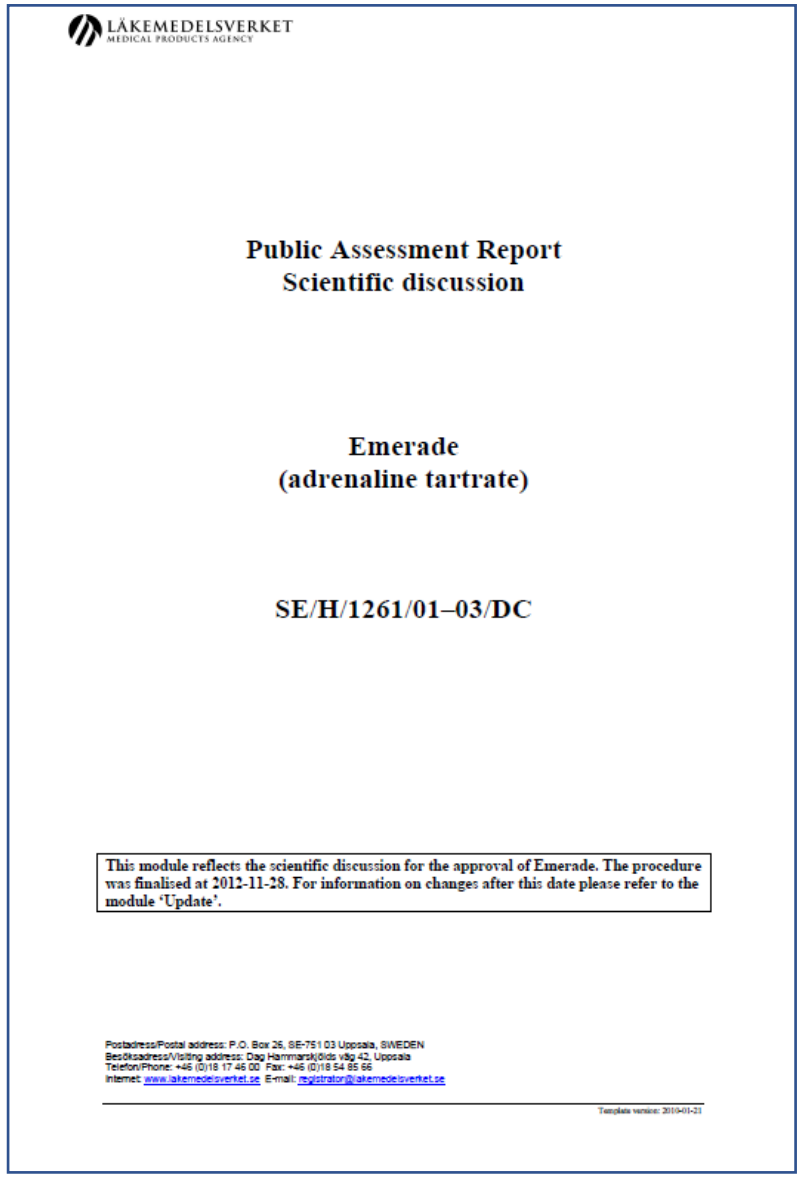

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Public Assessment Report
Scientific discussion

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'.

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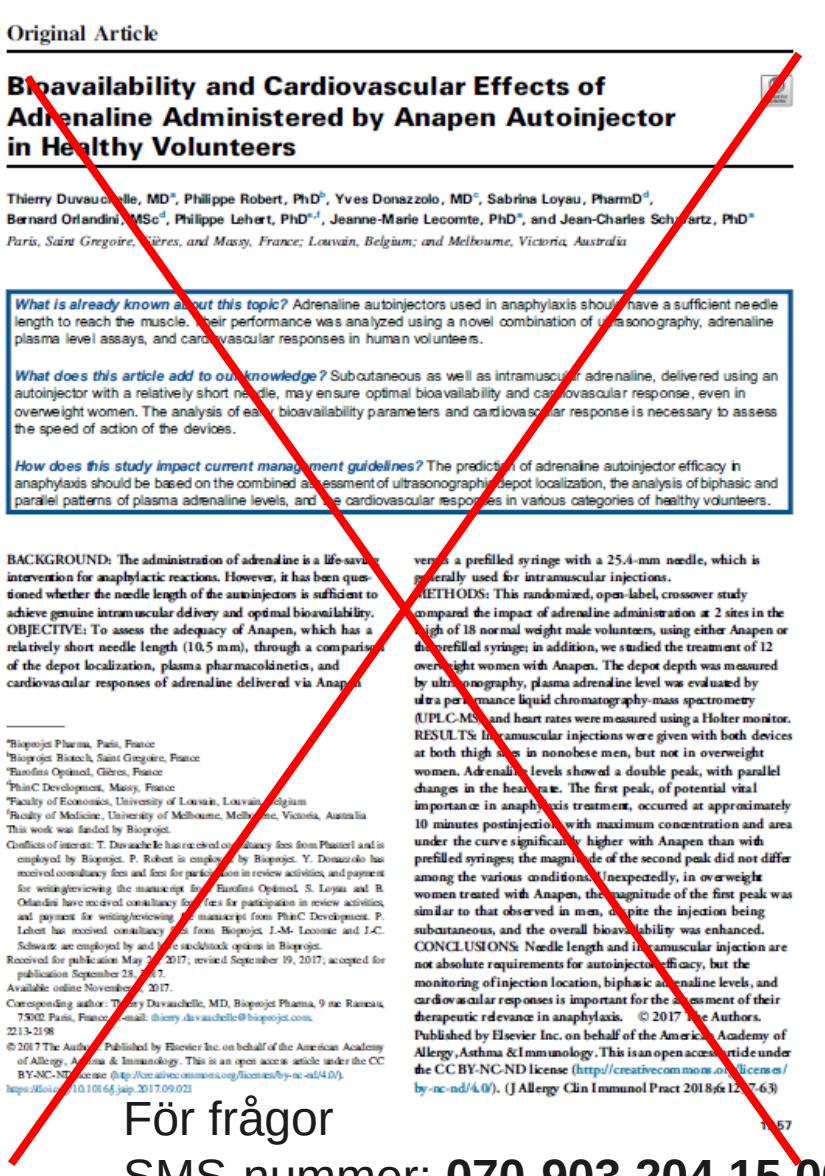

Original Article

Bioavailability and Cardiovascular Effects of Adrenaline Administered by Anapen Autoinjector in Healthy Volunteers

Thierry Duvauchelle, MD[a], Philippe Robert, PhD[b], Yves Donazzolo, MD[c], Sabrina Loyau, PharmD[d], Bernard Orlandini, MSc[d], Philippe Lehert, PhD[e,f], Jeanne-Marie Lecomte, PhD[a], and Jean-Charles Schwartz, PhD[a]
Paris, Saint Gregoire, Gières, and Massy, France; Louvain, Belgium; and Melbourne, Victoria, Australia

What is already known about this topic? Adrenaline autoinjectors used in anaphylaxis should have a sufficient needle length to reach the muscle. Their performance was analyzed using a novel combination of ultrasonography, adrenaline plasma level assays, and cardiovascular responses in human volunteers.

What does this article add to our knowledge? Subcutaneous as well as intramuscular adrenaline, delivered using an autoinjector with a relatively short needle, may ensure optimal bioavailability and cardiovascular response, even in overweight women. The analysis of early bioavailability parameters and cardiovascular response is necessary to assess the speed of action of the devices.

How does this study impact current management guidelines? The prediction of adrenaline autoinjector efficacy in anaphylaxis should be based on the combined assessment of ultrasonographic depot localization, the analysis of biphasic and parallel patterns of plasma adrenaline levels, and the cardiovascular responses in various categories of healthy volunteers.

BACKGROUND: The administration of adrenaline is a life-saving intervention for anaphylactic reactions. However, it has been questioned whether the needle length of the autoinjectors is sufficient to achieve genuine intramuscular delivery and optimal bioavailability.
OBJECTIVE: To assess the adequacy of Anapen, which has a relatively short needle length (10.5 mm), through a comparison of the depot localization, plasma pharmacokinetics, and cardiovascular responses of adrenaline delivered via Anapen versus a prefilled syringe with a 25.4-mm needle, which is generally used for intramuscular injections.
METHODS: This randomized, open-label, crossover study compared the impact of adrenaline administration at 2 sites in the thigh of 18 normal weight male volunteers, using either Anapen or the prefilled syringe; in addition, we studied the treatment of 12 overweight women with Anapen. The depot depth was measured by ultrasonography, plasma adrenaline level was evaluated by ultra performance liquid chromatography-mass spectrometry (UPLC-MS), and heart rates were measured using a Holter monitor.
RESULTS: Intramuscular injections were given with both devices at both thigh sites in nonobese men, but not in overweight women. Adrenaline levels showed a double peak, with parallel changes in the heart rate. The first peak, of potential vital importance in anaphylaxis treatment, occurred at approximately 10 minutes postinjection with maximum concentration and area under the curve significantly higher with Anapen than with prefilled syringes; the magnitude of the second peak did not differ among the various conditions. Unexpectedly, in overweight women treated with Anapen, the magnitude of the first peak was similar to that observed in men, despite the injection being subcutaneous, and the overall bioavailability was enhanced.
CONCLUSIONS: Needle length and intramuscular injection are not absolute requirements for autoinjector efficacy, but the monitoring of injection location, biphasic adrenaline levels, and cardiovascular responses is important for the assessment of their therapeutic relevance in anaphylaxis. © 2017 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/). (J Allergy Clin Immunol Pract 2018;6:1257-63)

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This work was funded by Bioprojet.
Conflicts of interest: T. Duvauchelle has received consultancy fees from Pfizer and is employed by Bioprojet. P. Robert is employed by Bioprojet. Y. Donazzolo has received consultancy fees and fees for participation in review activities, and payment for writing/reviewing the manuscript from Ineldea Optimed. S. Loyau and B. Orlandini have received consultancy fees, fees for participation in review activities, and payment for writing/reviewing the manuscript from PhinC Development. P. Lehert has received consultancy fees from Bioprojet. J.-M. Lecomte and J.-C. Schwartz are employed by and have stock/stock options in Bioprojet.
Received for publication May 2, 2017; revised September 19, 2017; accepted for publication September 28, 2017.
Available online November , 2017.
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2213-2198

https://doi.org/10.1016/j.jaip.2017.09.021

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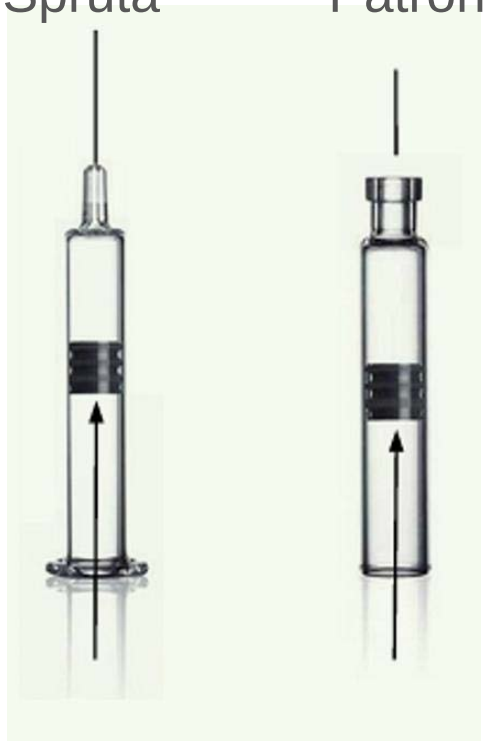
Emerade

EpiPen
Jext

Spruta

Patron



Nålen sitter fast på sprutan

Sprutan tål mindre injektions-kraft

Nålen är separerad från patronen

Patronen tål mer injektionskraft

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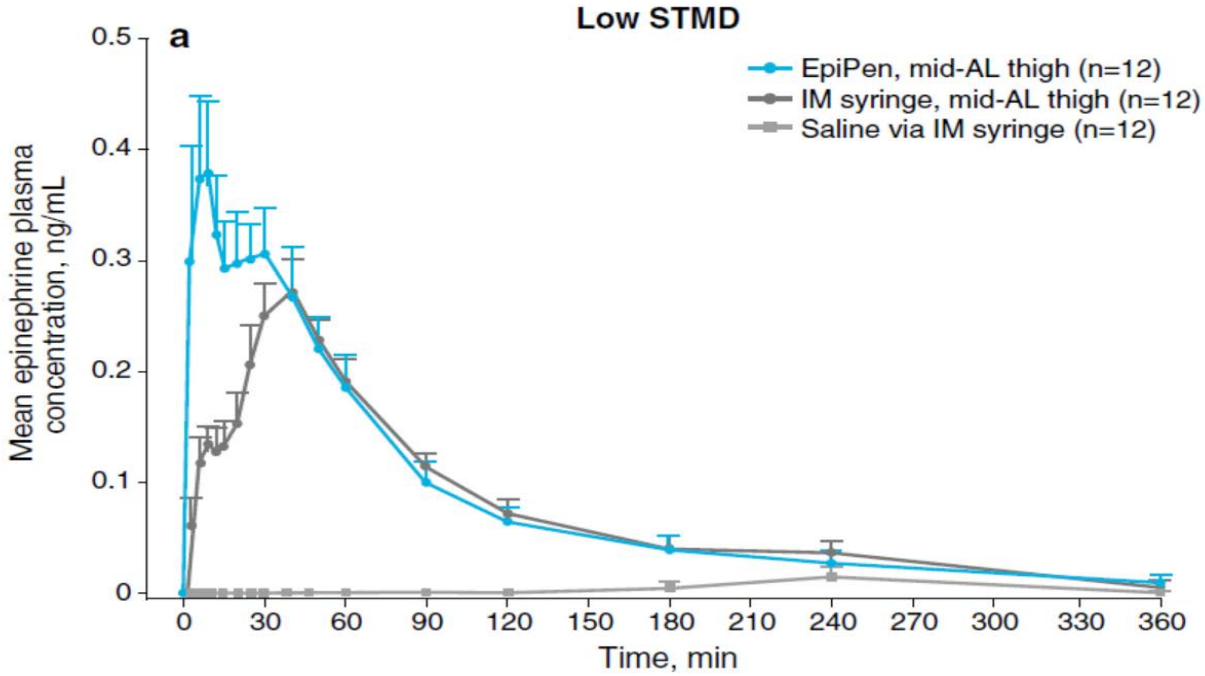
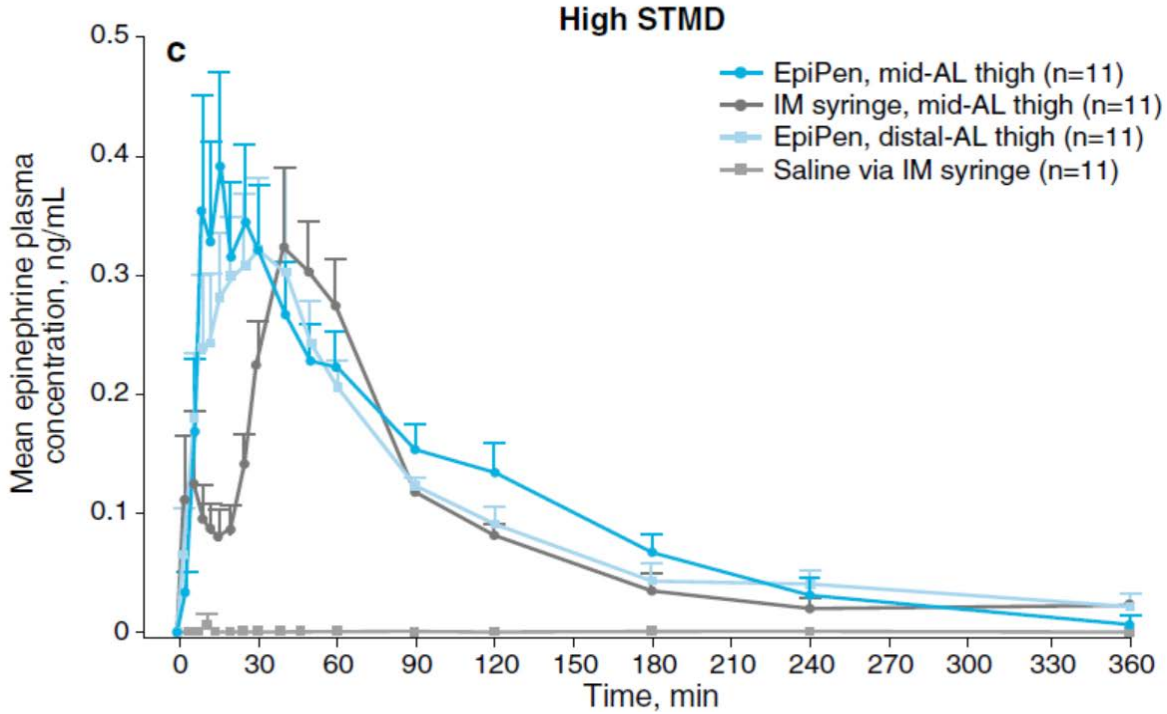
EpiPen resulterade i snabbare högre peakkoncentration av adrenalin jämfört med IM spruta och nål 25,4 mm i grupperna med lågt resp högt hud-till-muskeldiameter (STMD)

Viktigt på akuten





- Worm M et al. Clin Transl Allergy 2020;12:21

Anapen med kort nål jämfört med intramuskulär spruta och nål: samma resultat

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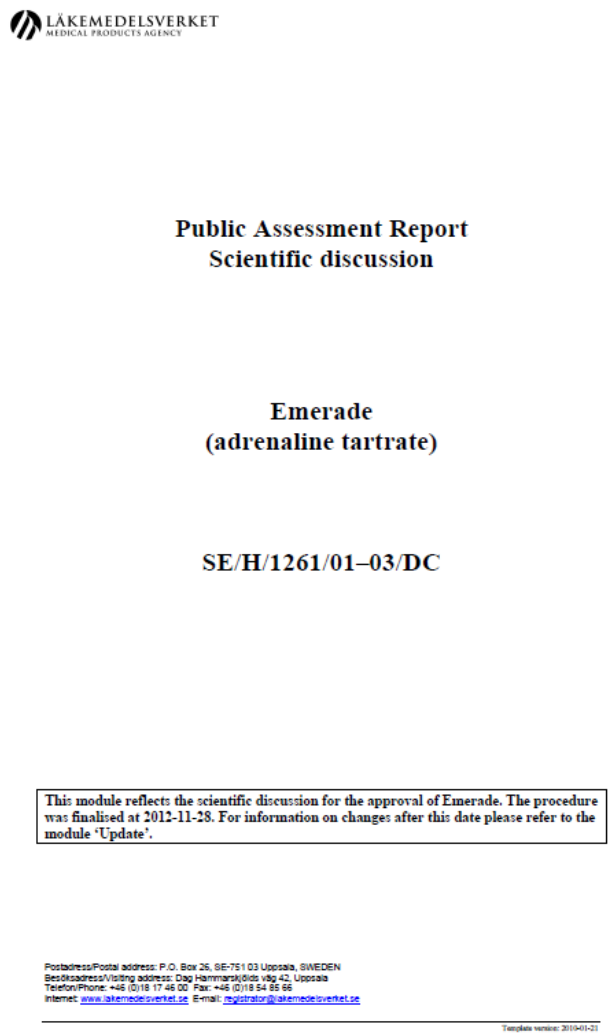

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(adrenaline tartrate)

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Emerade Study[2]

- 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:**

  1) Emerade 0.3mg
  2) Emerade 0.5mg
  3) Epipen 0.3mg *
  4) Jext 0.3mg *

- Public Assessment Report Sweden_Emerade_SE/H/1261/01-03/DC, 2018:
- https://docetp.mpa.se/LMF/Emerade%20solution%20for%20injection%20in%20pre-filled%20pen%20ENG%20PAR_09001bee807a122c.pdf accessed Feb 10, 2021

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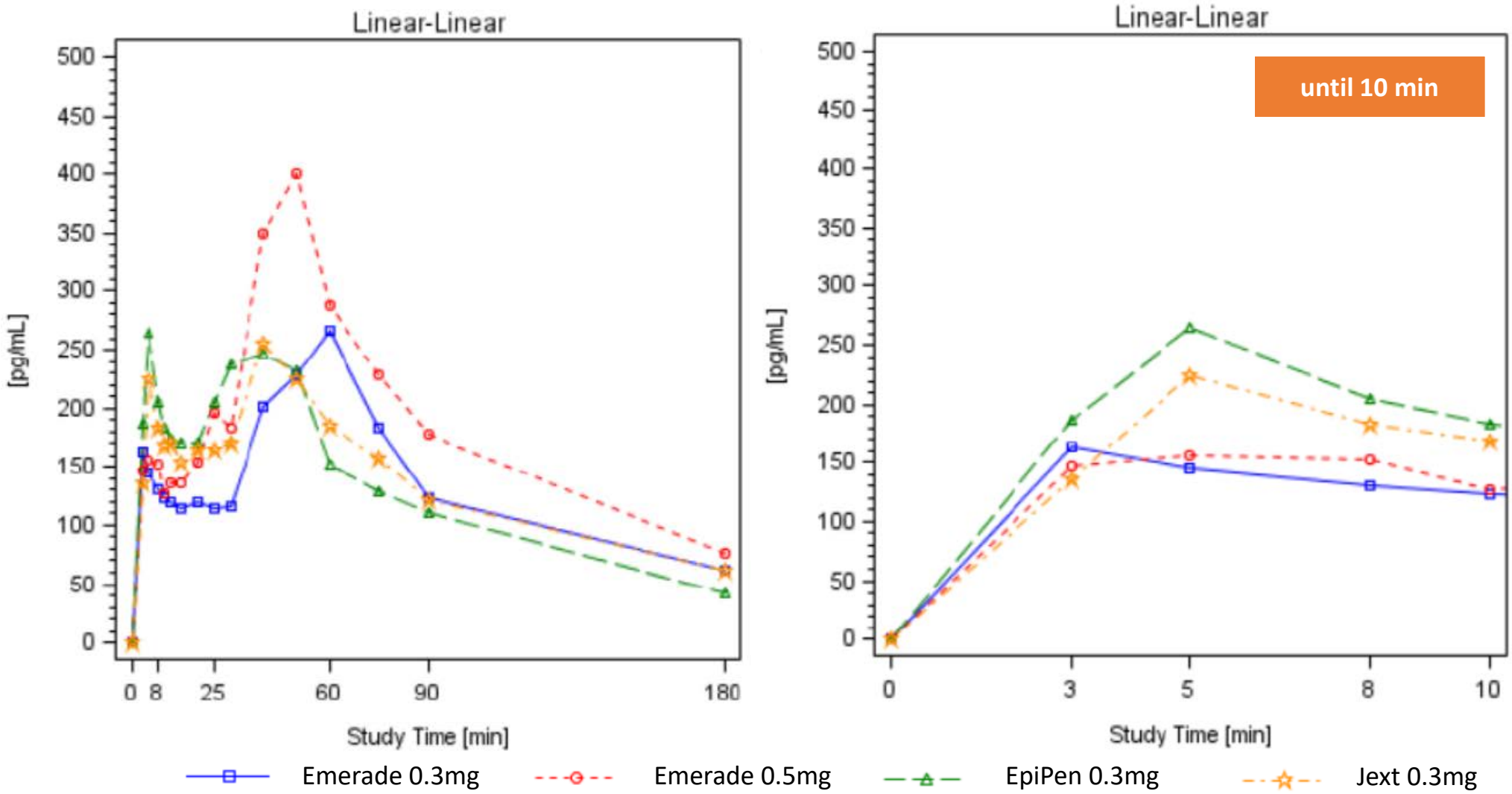
Cohort 1, STMD <15 mm (8 M, 7 K)



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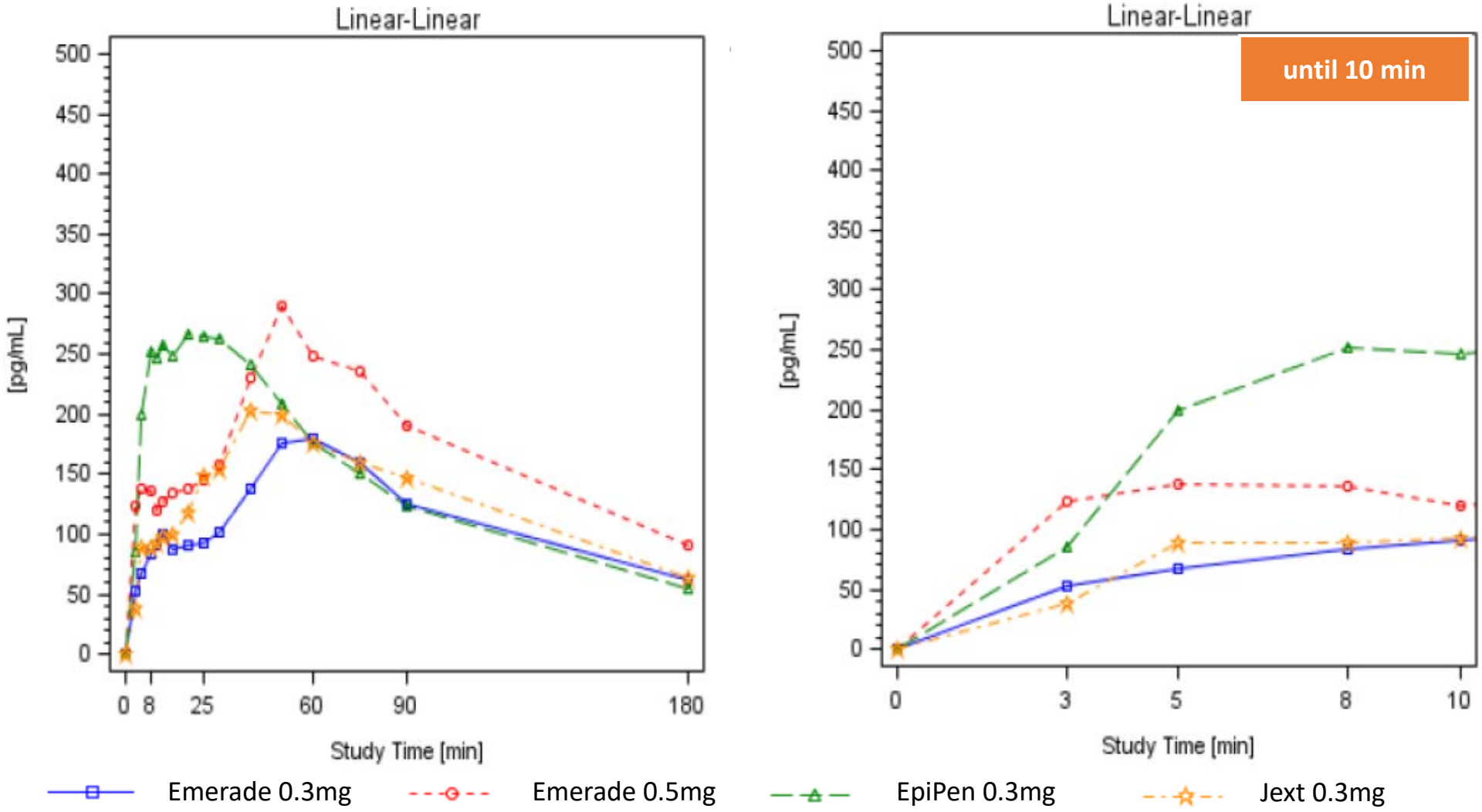
Cohort 2, STMD >15 mm & <20mm (8 M, 6 F)



Public Assessment Report Sweden_Emerade_SE/H/1261/01-03/DC, 2018: https://docetp.mpa.se/LMF/Emerade%20solution%20for%20injection%20in%20pre-filled%20pen%20ENG%20PAR_09001bee807a122c.pdf accessed Feb 10, 2021

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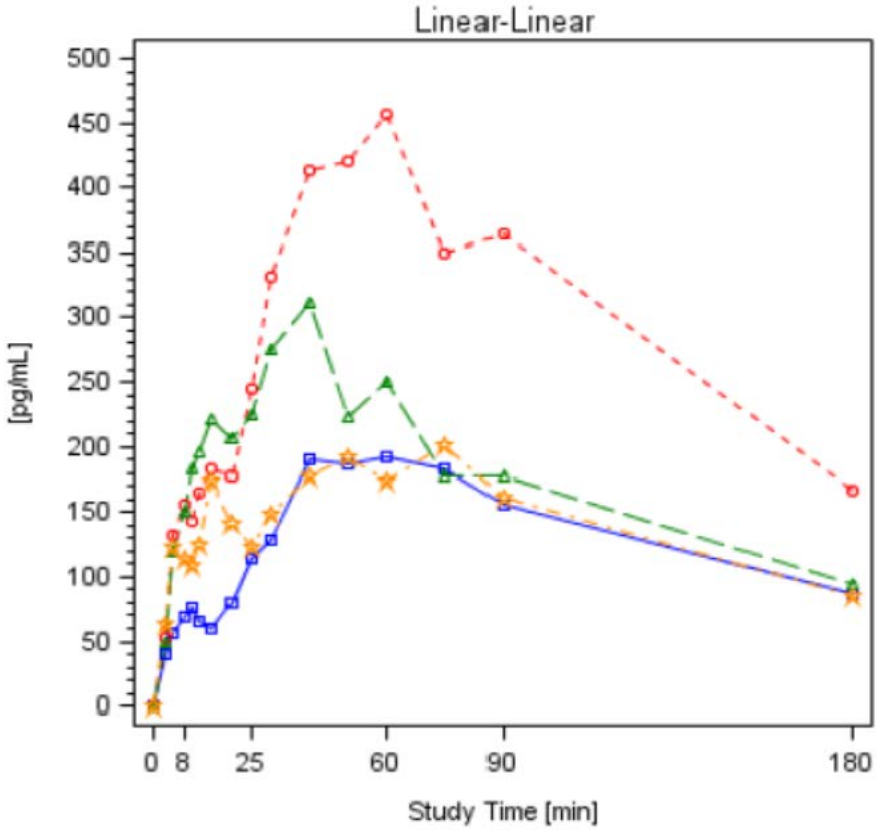
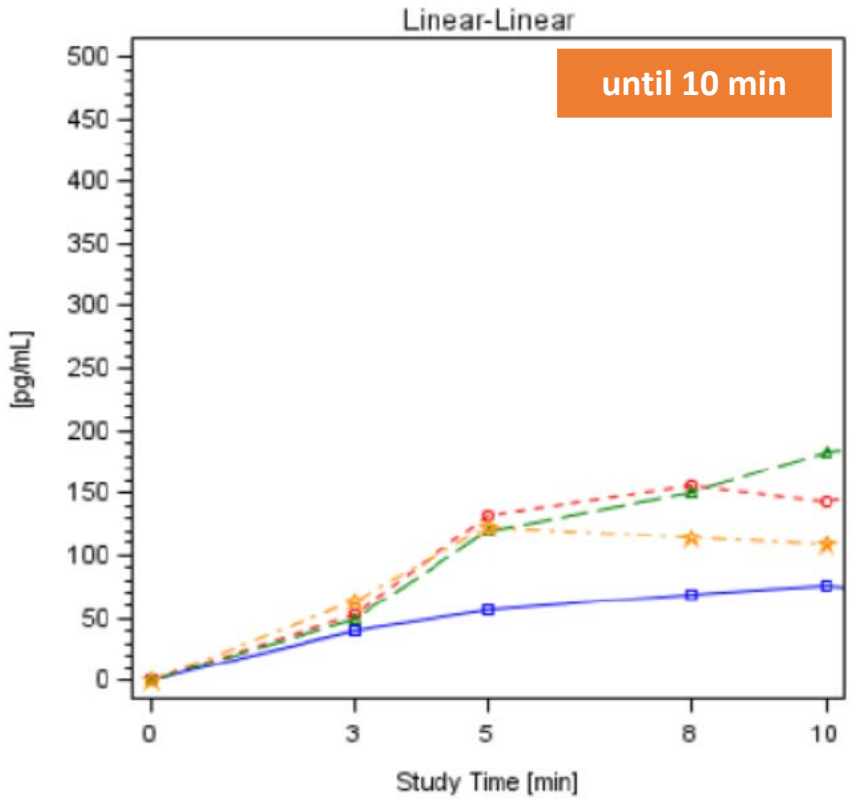
Cohort 3, STMD > 20 mm (6 F)





- De farmakokinetiska resultaten är varierande men indikerar att absorptionen är långsammare hos försökspersoner med stor stmd.
- Patronbaserade enheter (EpiPen) uppnådde högre adrenalinkoncentra-tioner inom de första 10 min
-

Emerade 0.3mg Emerade 0.5mg EpiPen 0.3mg Jext 0.3mg

Public Assessment Report Sweden_Emerade_SE/H/1261/01-03/DC, 2018: https://docetp.mpa.se/LMF/Emerade%20solution%20for%20injection%20in%20pre-filled%20pen%20ENG%20PAR_09001bee807a122c.pdf accessed Feb 10, 2021

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Advisary board gruppens kommentarer till studieresultaten

- Nållängden (Emerade) spelar obetydlig roll jämfört med autoinjektorns injektionskraft (EpiPen och Jext)
- En autoinjektor med patron och stark fjäder ger snabbast maxpeak (EpiPen)
- Maxpeaken bör infalla efter så tidigt som möjligt 5-10 min (EpiPen)
- Infaller den först efter 30 minuter finns risk för upprepade injektioner och risk för problematiska biverkningar inte minst om 0,5 mg ges (Emerade)
- 0,5 mg är inte en fördel annat än möjligen bland kvinnor > 80 kg
- Försiktighet med onödigt lång nål till magerlagda barn – benskada (Emerade)

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Hållbarhet som anges i april 2021

- EpiPen 24 mån
- Jext 22 mån
- Emerade 18 mån

Användarvänlighet

I Sverige 2014: 1 accidentell injektion i tummen

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Sammanfattning: Vilka faktorer kan vara av betydelse för en optimal och effektiv serumkoncentration

• Dos: 0,50 mg; >60 kg? (>80 kg Kvinnor)	1 g, dvs två injektioner kan vara för hög dos för vissa (Emerade)
• Injektionskraft	Patronladdad penna bäst dvs Epipen/Jext
• Nållängd	Spelar ingen roll i samman-hanget, men risk för benskada om lång nål till magerlagda barn
• Hållbarhet	Epipen bäst hållbarhet
• Användarvänlig	Sannolikt Emerade
• Förvaring	Samtliga inte > 25°C

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Kraftigare fjäder
Bättre injektionskraft

Smidighet

Mer otymplig
Mindre tydlig

Svagare fjäder
Sämre injektionskraft

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