American Academy of Allergy Asthma & Immunology
ANNUAL MEETING
WASHINGTON, DC · FEBRUARY 23-26, 2024

Bioavailability and stability of an Epinephrine Nasal Powder Formulation for Treatment of Anaphylaxis

M. Jönsson[1], J. Sävmarker[1], J. Rudén[1], D. Öhlund[1], R. Coburn[2], R. Rönn[1]

Presented by: Dr Anne K. Ellis[3]

1) Orexo AB; 2) Orexo US Inc; 3) Department of Medicine, Queen's University

American Academy of Allergy Asthma & Immunology
ANNUAL MEETING
WASHINGTON, DC · FEBRUARY 23-26, 2024

Disclaimer

I am a Professor and Chair of the Division of Allergy and Immunology in the Department of Medicine at Queen's University and the Director of the Environmental Exposure Unit and Allergy Research Units at Kingston General Hospital in Canada.

I am presenting these data and results as a medical and scientific advisor to Orexo AB. Any opinions about the data and results discussed today are not that of the University, Kingston General Hospital, or Orexo AB but are mine and mine alone.

American Academy of Allergy Asthma & Immunology
ANNUAL MEETING
WASHINGTON, DC · FEBRUARY 23-26, 2024

Presenter Disclosures (Other)

Advisory Boards	ALK Abello, ARS, AstraZeneca, Aralez, Bausch Health, Circassia Ltd, GlaxoSmithKline, Johnson & Johnson, Merck, Mylan, Novartis, Pediapharm and Pfizer
Speaker Bureaus	ALK, Aralez, AstraZeneca, Boerhinger-Ingelheim, CSL Behring, CACME, Meda, Mylan, Merck, Novartis, Pediapharm, Pfizer, The ACADEMY, and Takeda
CME Activities	CSACI Annual Planning Committee
Research Grants	AllerGen NCE, CIHR, JP Bickell Medical Foundation, CITF, PSI (to Institution)
Research Grants from Private Industries or Non-profit Funds	My institution has received research grants from ALK, AstraZeneca, Bayer LLC, Circassia Ltd, Green Cross Pharmaceuticals, GlaxoSmithKline, Sun Pharma, Merck, Novartis, Pfizer, Regeneron, Reve Pharmaceuticals and Sanofi

American Academy of Allergy Asthma & Immunology
ANNUAL MEETING
WASHINGTON, DC · FEBRUARY 23-26, 2024

Background

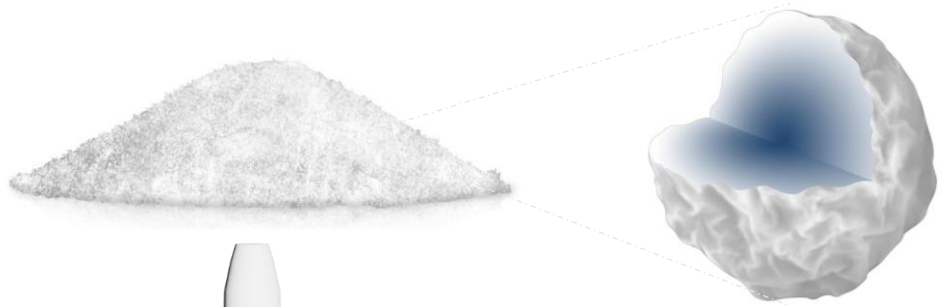
Unmet medical need with current epinephrine auto-injectors for treatment of anaphylaxis:

Medical need	**Potential issues with autoinjectors**
The product needs to be available	Bulky packaging and restrictive storage conditions may limit carrying of the product
The product needs to be used	Invasive route of administration may deter timely use Needle phobia may be an issue in patients
The product needs to be effective	Auto-injectors have limited shelf-life (esp. if stored improperly)
The product needs to be safe	Accidental finger and bone injections Preservatives/antioxidants needed for stability

American Academy of Allergy Asthma & Immunology
ANNUAL MEETING
WASHINGTON, DC · FEBRUARY 23-26, 2024

Epinephrine as an amorphous nasal powder

- A spray-dried homogenous powder, including epinephrine and excipients in composite amorphous particles



- A commercially available single-dose administration device

- A compact storage tube with built-in moisture protection

American Academy of Allergy Asthma & Immunology
ANNUAL MEETING
WASHINGTON, DC · FEBRUARY 23-26, 2024

Bioavailability study

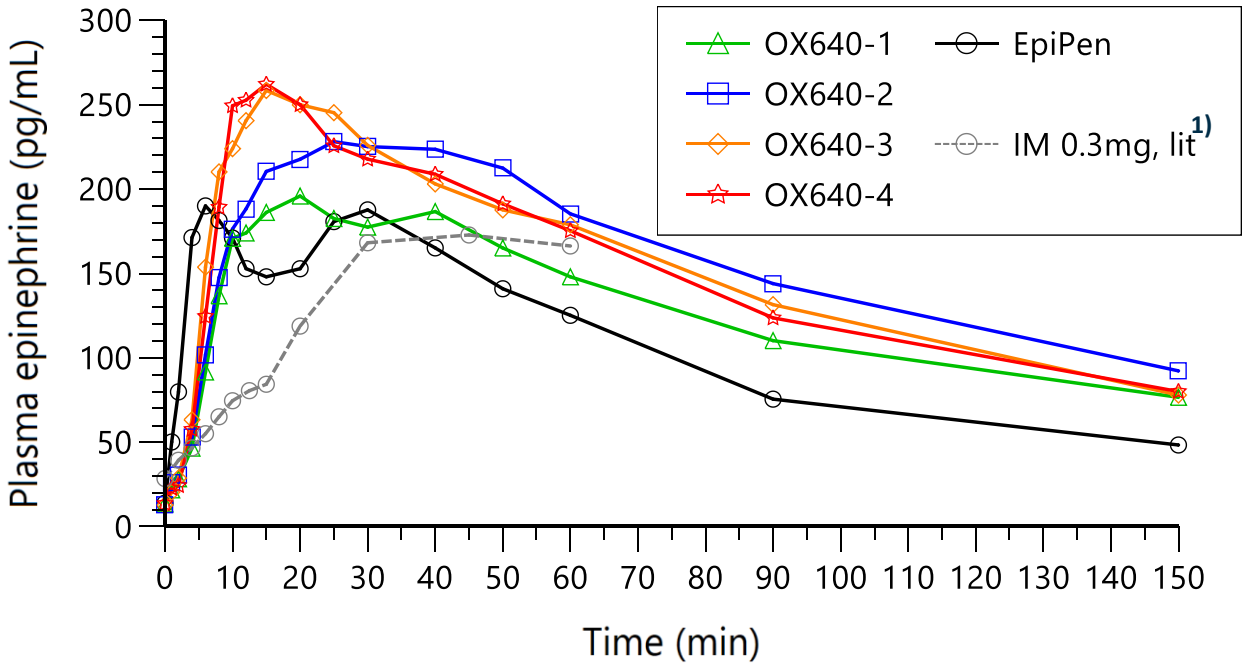
American Academy of Allergy Asthma & Immunology
ANNUAL MEETING
WASHINGTON, DC · FEBRUARY 23-26, 2024

Study design

- A 5-period, cross-over, pharmacokinetic study in 40 healthy volunteers
- Four investigational powder formulations, **OX640**-1 to -4 containing 1 mg epinephrine vs **EpiPen®** 0.3 mg dosed in a randomized sequence
- PK sampling at 21 sampling timepoints (including 3 baseline samples) until 360 min (6h) after dose, with frequent initial sampling
- Blood pressure and heart-rate were measured as pharmacodynamic parameters at the time of blood sampling

American Academy of Allergy Asthma & Immunology
ANNUAL MEETING
WASHINGTON, DC · FEBRUARY 23-26, 2024

Pharmacokinetic results

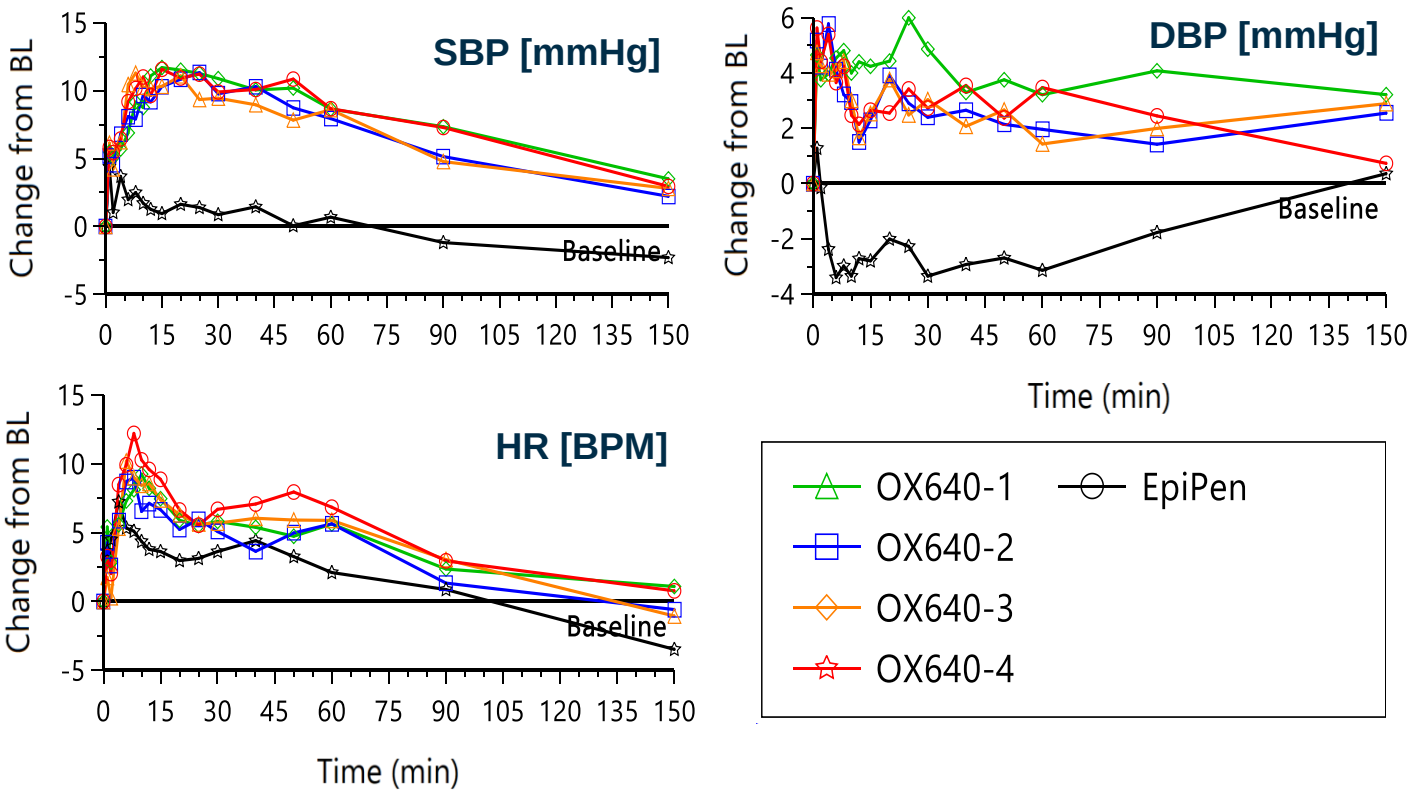


- Peak and early exposure (0-20 min) was comparable between **OX640** and **EpiPen®**, while total exposure was somewhat higher for **OX640**
- **EpiPen®** displayed the most rapid initial absorption, with nasal formulations catching up within 8-10 min
- Early **OX640** exposure may be bracketed between **EpiPen®** and IM 0.3 mg given by manual syringe[1] (comparison to literature)
- Of the **OX640** formulations, **OX640**-3, and -4 appeared more rapid than -1 and -2

1) FDA Briefing Document, Pulmonary-Allergy Drug Advisory Committee Meeting, May 11, 2023

American Academy of Allergy Asthma & Immunology
ANNUAL MEETING
WASHINGTON, DC · FEBRUARY 23-26, 2024

Pharmacodynamic results



- **OX640** formulations produced a rapid increase in blood pressure and heart rate
- Blood pressure effects were higher from nasal formulations than from **EpiPen®** throughout the sampling period
- Results support a comparable onset of desired vasopressor effects to EpiPen (despite differences in early exposure)

Safety results

- **OX640** formulations and **EpiPen®** demonstrated a similar systemic safety profile, with typical sympathomimetic side effects, including headache, palpitations, tremor, hypoesthesia and hypervigilance being most common
- One subject was discontinued due to reoccurring ECG changes after dosing (prolonged QRS complex after both **EpiPen®** and **OX640** administration)
- Most subjects reported local discomfort in connection with nasal dosing, typically mild nasal stinging/burning

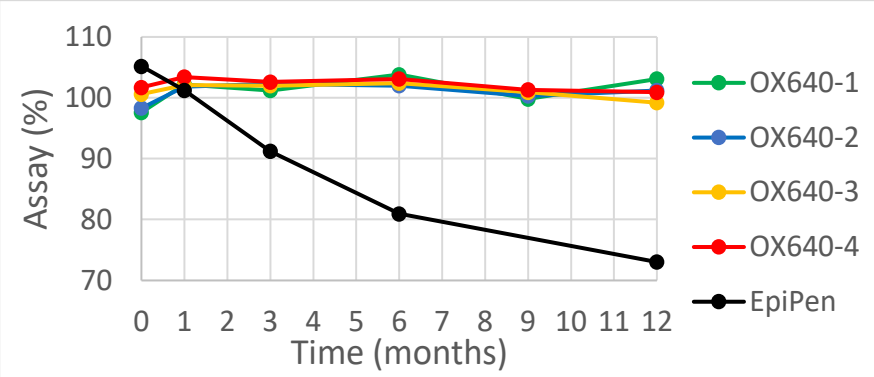
American Academy of Allergy Asthma & Immunology
ANNUAL MEETING
WASHINGTON, DC · FEBRUARY 23-26, 2024

Stability data

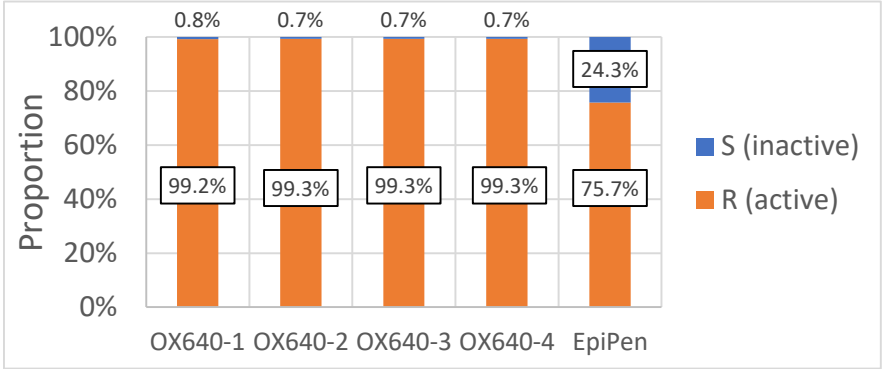
American Academy of Allergy Asthma & Immunology
ANNUAL MEETING
WASHINGTON, DC · FEBRUARY 23-26, 2024

Chemical stability at 40°C (104°F)

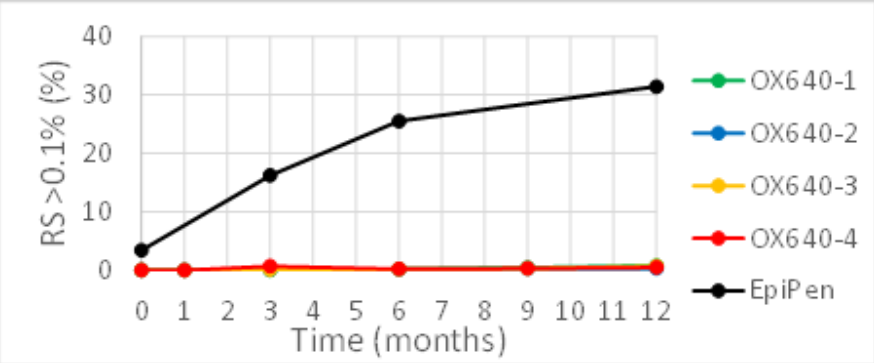
Epinephrine content, 40°C/ 75% RH



Enantiomeric purity, 12 months, 40°C/ 75% RH



Epinephrine degradation products 40°C/ 75% RH

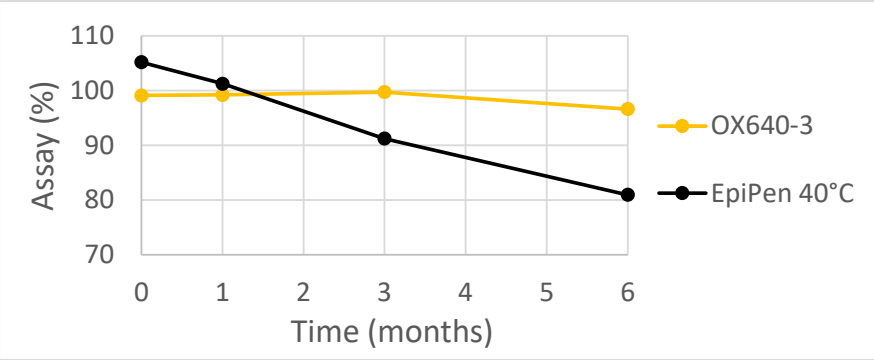


- Epinephrine degradation was substantial in the aqueous **EpiPen®** formulation:
  - Decrease in assay from 105 to 73% with associated increase in degradation products (RS)
  - An enantiomeric purity of only 76% at 12 months
  - ➢ **~55% of the nominal dose remaining at 12 months**
- Minimal degradation and racemization of **OX640** powder formulations over 12 months, with full strength maintained

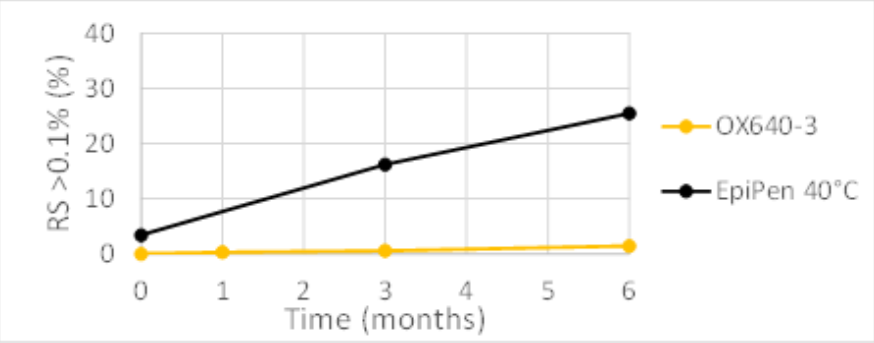
American Academy of Allergy Asthma & Immunology
ANNUAL MEETING
WASHINGTON, DC · FEBRUARY 23-26, 2024

Chemical stability at 50°C (122°F)

Epinephrine content, 50°C



Epinephrine degradation products, 50°C

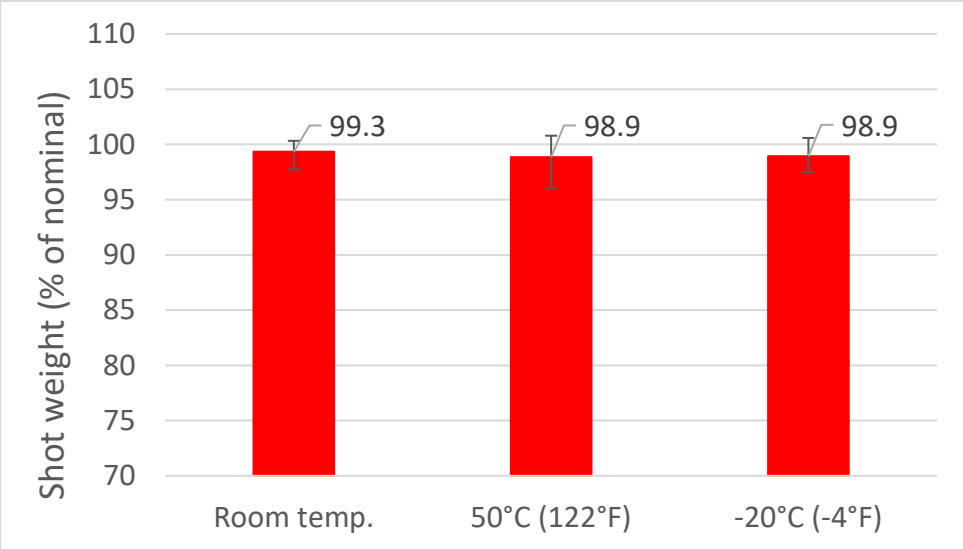


- 6-month data at 50°C for formulation OX640-3
- EpiPen data at 40°C was included for reference
- Results indicate excellent stability of powder formulations also at 50°C, with <3% degradation over 6 months

American Academy of Allergy Asthma & Immunology
ANNUAL MEETING
WASHINGTON, DC · FEBRUARY 23-26, 2024

Shot weight at different temperatures

Emitted shot weight at different temperatures



Error bars represent range

- To assess device performance, at different temperatures, emitted shot weights of formulation OX640-3 was assessed after overnight storage in RT, 50°C (122°F) and -20°C (-4°F), n=7 per condition
- The full dose was delivered at all tested temperatures, supporting that the product was operational over the entire temperature range

American Academy of Allergy Asthma & Immunology
ANNUAL MEETING
WASHINGTON, DC · FEBRUARY 23-26, 2024

Concluding remarks

American Academy of Allergy Asthma & Immunology
ANNUAL MEETING
WASHINGTON, DC · FEBRUARY 23-26, 2024

Concluding remarks…

- In this study OX-640 showed comparable PK and PD data to EpiPen and IM Epinephrine
- The stability of OX-640 is far superior to the EIA's currently on the North American Market
- Thus, OX-640 has the potential to be a safe and effective epinephrine delivery device