

SWIFTARC: Salmeterol With Fluticasone for Altitude Related Conditions

A Phase 1/2a Study Testing Safety, Tolerability and Efficacy of Inhaled Salmeterol and Fluticasone in Resting and Hypoxia-Exercising Subjects to Improve High Altitude Performance

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MTEC
Medical Technology
Enterprise Consortium



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Disclosures/Conflicts of Interest

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Assets are Needed to Improve High Altitude Tolerance in Warfighters



High altitude US military operations are likely in future

- Severe high altitude pulmonary edema (HAPE) occurs in 1-5% & requires evacuation
- Subclinical pulmonary edema may occur in all: ↓ performance
- Meds to prevent severe illness & improve exercise capacity at altitude are important assets



High altitude illness often requires evacuation

- Risks more lives
- Prevention is thus key

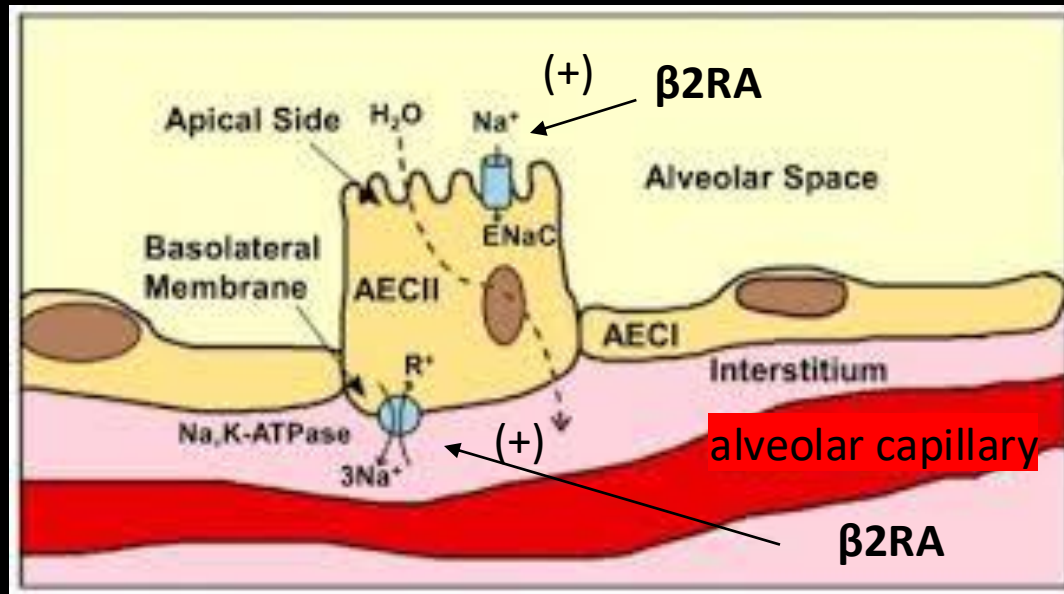


Several medications decrease subclinical pulmonary edema at altitude & improve performance

But: therapies embraced in civilian world to improve high altitude tolerance & prevent HAPE are less appealing in military operations

- Steroids
- PDE5 inhibitors (sildenafil, etc.)

Salmeterol ($\beta 2R$ agonist) - Compelling Mechanism to Keep Lung Alveoli Dry at High Altitude



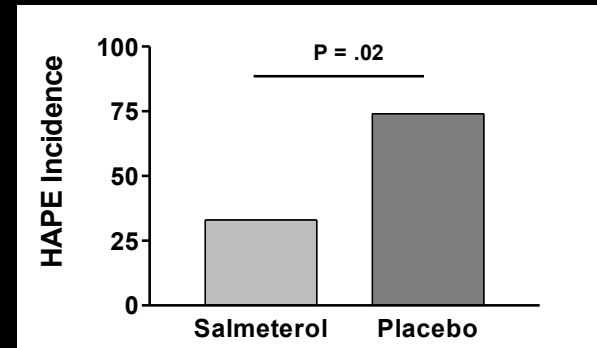
AECI: type I alveolar epithelial cell
AECII: type II alveolar epithelial cell

Epithelial Sodium Channel (ENaC) and basolateral Na/K ATPase: keep the alveolus stay dry

- $\downarrow$ activity leads to $\uparrow$ alveolar/pulmonary edema
 - o Hypoxia $\downarrow$ activity (endocytosis in minutes/hours) as they are heavy ATP consumers during normoxia
 - o reverts to normal state w/ reoxygenation
 - o Steroids $\uparrow$ NA/K ATPase/ENaC expression & blunt hypoxic endocytosis
- Inhaled $\beta 2R$ agonists $\uparrow$ NA/K ATPase & ENaC activity (whatever remains on cell membrane)

Inhaled Salmeterol (long-acting β -2R agonist) is a Compelling Drug to Prevent HAPE & Improve High Altitude Performance

- Salmeterol (an inhaled β 2RA) prevented HAPE at high altitude in a small placebo-controlled RCT*
 - 37 known HAPE-susceptible subjects
 - Study drug day prior to ascent, and for 2d at altitude
 - **Dose = 3x of highest FDA-approved dose for asthma/COPD (125 ug = 6 puffs, BID)**
 - Salmeterol was highly effective



- **But - Safety Data was nearly absent**
 - Known β 2RA side effects: hypokalemia, QTc prolongation, cardiac tachyarrhythmias/ectopy, tremor
 - Thus, expert guidelines such as the Wilderness Medical Society do not recommend it
- Note: long-acting inhaled β 2R agonists (LABA) in MDI now only available mixed w/ corticosteroids (ICS)

* Sartori 2002; NEJM 346:1631-36

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3 Clinical Studies (all placebo-controlled, randomized, cross-over trials)



**“Study 1” - Healthy Controls
high dose inhaled salmeterol/ICS**

- Phase 1: Safety/Tolerability
- Phase 2: Efficacy (VO₂max)

Today's Talk – Unblinded Data



**“Study 2” – HAPE Susceptible
high dose inhaled salmeterol/ICS**

- Phase 1: Safety/Tolerability
- Phase 2: Efficacy (VO₂max)

Half Complete – Blinded Data



**“Study 3” – HAPE Susceptible
combo salmeterol/ICS & Nifedipine**

- Phase 1: Safety/Tolerability
- Phase 2: Efficacy
- Hypoxia chamber stay

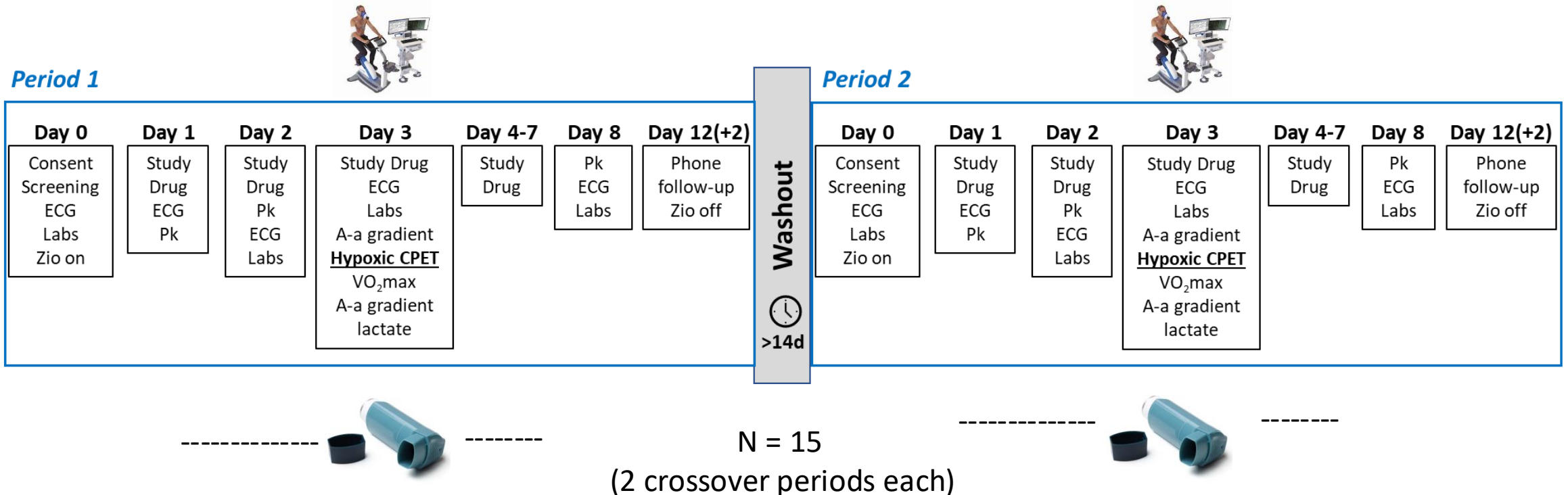
Upcoming 1/2027

Design of SWIFTARC “Study 1”

Healthy Controls (Denver metro area)

Phase 1b: Safety/Tolerability; primary outcome

Phase 2a: efficacy (hypoxic exercise VO₂ max)]



Zio = cardiac patch for continuous arrhythmia monitoring

Pk = Pharmacokinetics

CPET = cardiopulmonary exercise test

FiO₂ on CPET Day (“Pike’s Peak”)

30 min “ascent” to FIO₂ 14% (PaO₂ = 40 mmHg)

2 hr at 14%; then max effort CPET at 14%

Simulate helicopter lift to high altitude, exertion

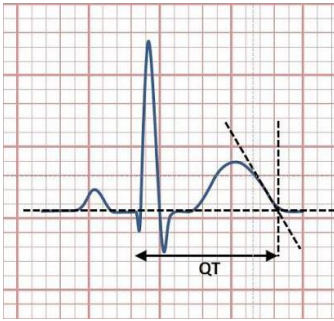
Study 1 Highlights

- Enrollment began early 2024; completed Summer 2026
- Local/HRPO IRB-approved
- Registered Clinical trials.gov (NCT06040268)
- Careful inclusion/exclusion criteria (age < 50, BMI < 35, no CV disease, etc)
- DSMB oversight, stopping rules in place
- Extensive safety monitoring
- FDA oversight (IND 168356)

Safety/Tolerability Monitoring for Side-Effects in Study 1 based on known LABA side effects

CV

- Heart rate $\uparrow$ *¶
- Ectopy $\uparrow$ *
- Tachyarrhythmias*
- QTc $\uparrow$ ¶



* by Ziopatch

¶ By 12-lead EKGs

Metabolic

- Serum [K+] $\downarrow$
- Serum [glucose] $\uparrow$

Other Symptoms

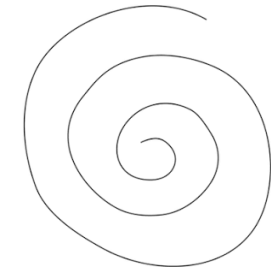
- Likert scale
 - Shakiness
 - Insomnia
 - Palpitations
 - Sleep

Tremor

- Likert scale (subjective)
- Hand tremor (objective)



accelerometry



draw spirals

Subject Demographics – SWIFTARC Study 1

N	15
Age (years, mean)	34.3
Gender (% Female)	67%
Competitive Athletes	53%
<u>Ethnicity</u>	
White, non-Hispanic	12
Hispanic	3
African-American	0
Other	0

Unblinded Results: High dose inhaled salmeterol, (with normal dose fluticasone) is safe and tolerable over a week & during 3 hours of hypoxia (w/ exercise)

Serious Adverse Events: None

Cardiovascular

- HR: Minimal ↑ (4-7 bpm) thru d8
- Ectopy: not significant (NS)
- Tachyarrhythmias: NS
 - Occasional SVT, NSVT – placebo too
 - No atrial fibrillation, no VT
- All QTc met safety cutoffs: 450 msec ♂
470 msec ♀
 - QTc 8-16 msec ↑ at 1/2/6 hrs w/ drug on PK day
 - CPET: NS

Metabolic

- [K+] ↓: rare lows, mild shifting
- Glucose: mild ↑ (11 mg/dL at 90 mins)

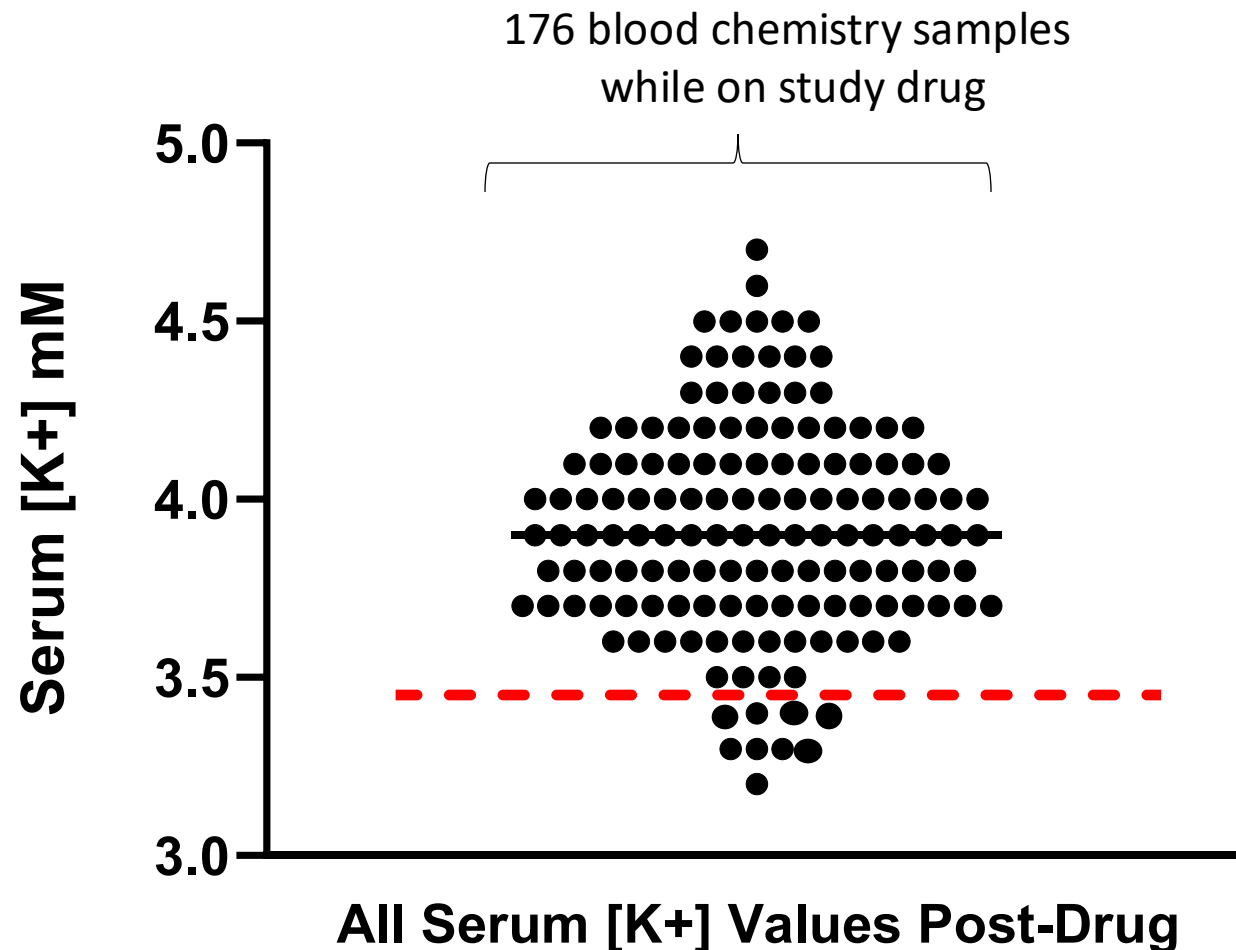
Tremor (spirals, accelerometry)

- Mild ↑ at 30, 60 min after drug
 - Maximum relative ratio = 3

Overall Symptoms

- All NS except day 2 shakiness ↑ slightly 30 min after drug

Serum Potassium Results: Drug – related Hypokalemia is Uncommon



Mild hypokalemia: 9 episodes

- [3.2] mM: 1 (lowest)
- [3.3] mM: 4 (2 in placebo arm)
- [3.4] mM: 4
- 3 were in one person
- All asymptomatic

[K] Shift: 0.24 mM maximum ↓ at 90 mins

- $P < 0.01$
- NS at 30 mins, 6 hrs
- rare muscle cramping

Efficacy: VO_2 Max Results (Hypoxic VO_2max , 13% FiO_2 Target)

- Every subject completed a CPET (3/15 only completed one CPET)
 - 2 vagal RXNs, 1 migraine
- VO_2 Max range: 20-43.3 ml $\text{O}_2/\text{kg}/\text{min}$
 - Intra-individual difference between periods: mean 3.5 ml/kg/min (range 0.2 – 5.2)
 - Mixed methods analysis: VO_2max placebo vs drug: Not significant
 - Strong trend ($p = .06$) for higher pH at max exercise with study drug
- No drug-related change in ectopy or tachyarrhythmias during 2.5 hrs hypoxia/hypoxic CPET



Conclusions

- **High dose inhaled salmeterol (with fluticasone) is safe and tolerable** in young/middle-aged healthy control subjects
 - During 1 week of use at Denver altitude (5,280 ft)
 - During 2.5 hours of hypoxia simulating 14,000 feet
 - During hypoxic exercise
- High dose inhaled salmeterol (with fluticasone) is a safe and tolerable option to prevent HAPE in warfighters during high altitude missions, or in civilians during high altitude travel
- High dose inhaled salmeterol (with fluticasone) does not improve hypoxic exercise VO_2 Max in healthy controls
 - Study 2 will evaluate this in HAPE-susceptible subjects
- SWIFTARC study 2 half completed – assessing high dose inhaled salmeterol (with fluticasone) in known HAPE susceptible subjects
 - no SAE, no obvious safety or tolerability signals
 - will present unblinded results at MHSRS 2027

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