Absorption, Distribution, Metabolism, and Excretion (ADME) Supports SENS-401 as Orally-Active Otoprotectant

Jonas Dyhrfjeld-Johnsen, PhD[1]; Sonia Poli, PhD[2]; Pierre Attali, MD, MSc[1]
[1]Sensorion SA, [2]Poli Consulting

Study objectives:

1. Determine preclinical pharmacokinetics and local exposure of racemic (R/S) azasetron (SENS-218) and the pure (R)- (SENS-401) and (S)-enantiomers.
2. Compare single enantiomer plasma pharmacokinetics after administration of the marketed racemate, SENS-218 to healthy volunteers

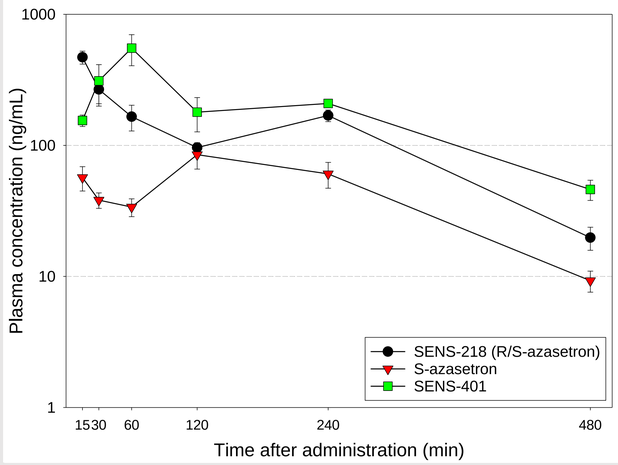
Methods:

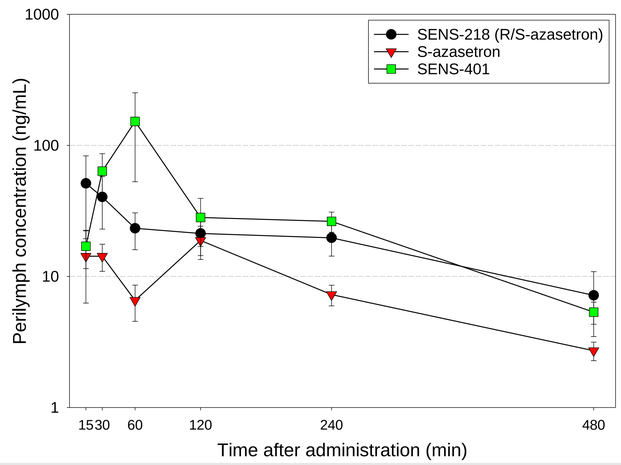
Wistar rats (n=4/group) received either 10 or 100 mg/kg SENS-218 or 10 mg/kg SENS-401 or (S)-enantiomer orally with subsequent blood, perilymph and inner ear tissue sampling.

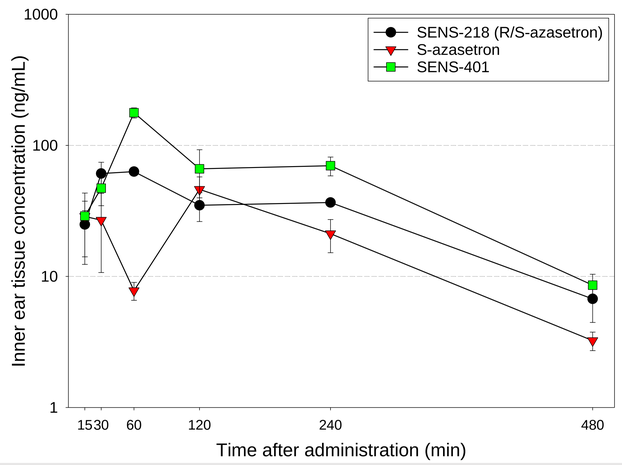
Healthy volunteers (n=24) received a single 20 mg oral dose of SENS-218 with subsequent blood sampling.

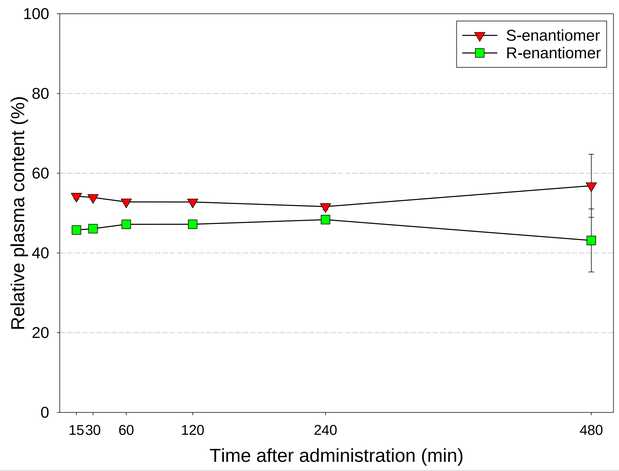
(R)-, (S) and (R/S)-azasetron concentrations were quantified by LC-MS/MS and analyzed in Phoenix WinNonLin.

SENS-401 (R-azasetron besylate) demonstrates better oral absorption and higher inner exposure (perilymph, inner ear tissue) than SENS-218 (R/S-azasetron HCl) and S-azasetron after single, base-equivalent (9.1 mg/kg) doses administered orally to male Wistar rats.

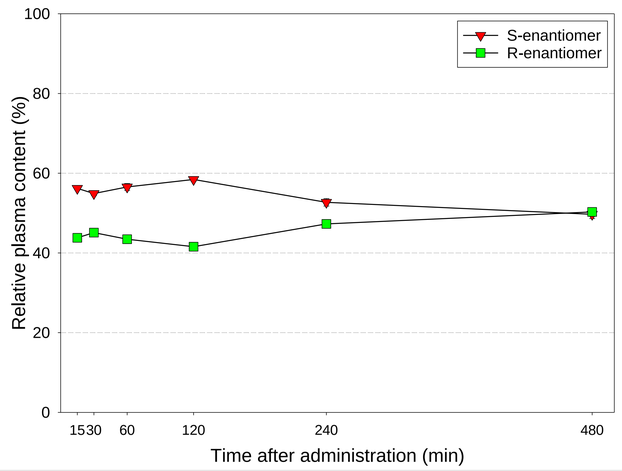


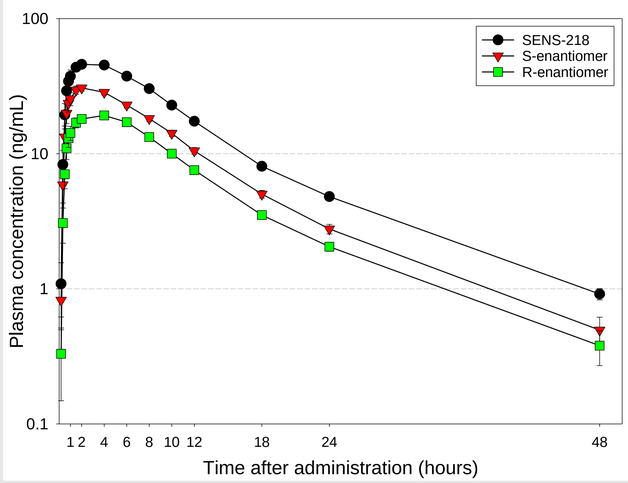




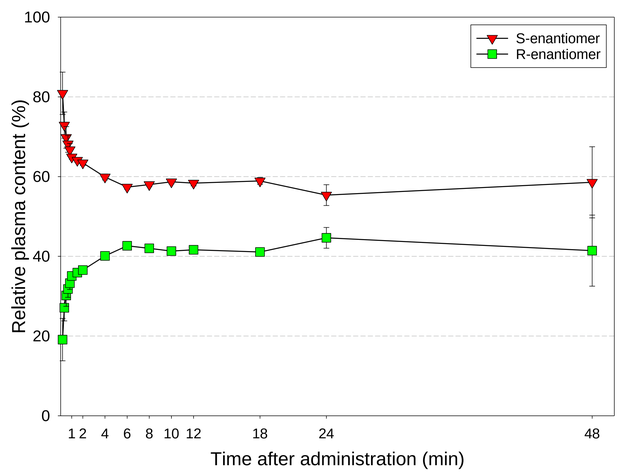


Following single oral administration of 10 mg/kg (left) or 100 mg/kg (right) SENS-218 (racemate) to male Wistar rats, the mean relative plasma content of the S-enantiomer was consistently slightly higher (54-55%) than for the R-enantiomer (45-46%).





Following a single oral 20 mg dose of SENS-218 (R/S-azasetron) in healthy Caucasian volunteers, pharmacokinetics mirror Asian published data. As in rat, the the S-enantiomer mean relative plasma content of was consistently higher than for the R-enantiomer. After 4 hours, the S:R ratio was 58 % to 42%.



CONCLUSIONS

- The higher local exposure in the inner ear of SENS-401 is consistent with superior treatment effects obtained in pre-clinical models of sudden sensorineural hearing loss.
- The clinically reproducible lower exposure of (R)- vs (S)-enantiomer after SENS-218 administration is consistent with lower local exposure of SENS-218 in rat and supports development of the pure SENS-401 R-enantiomer as otoprotective treatment to ensure optimal local drug exposure and treatment effect for patients.
- SENS-401 has received orphan drug designation for the treatment of Sudden Sensorineural Hearing Loss (EMA) and Platinum-Induced Ototoxicity (FDA).
- A randomized double-blind, multiple ascending dose Phase 1 study of SENS-401 in healthy volunteers has recently been completed (ClinicalTrials.gov : NCT03071003) and SENS-401 shown to be well tolerated.

CONTACT

Dr. Jonas Dyhrfjeld-Johnsen
Sensorion SA
Email:
jonas.dyhrfjeld-Johnsen@sensorion-pharma.com
Website:
www.sensorion-pharma.com