RS-2024-00349857

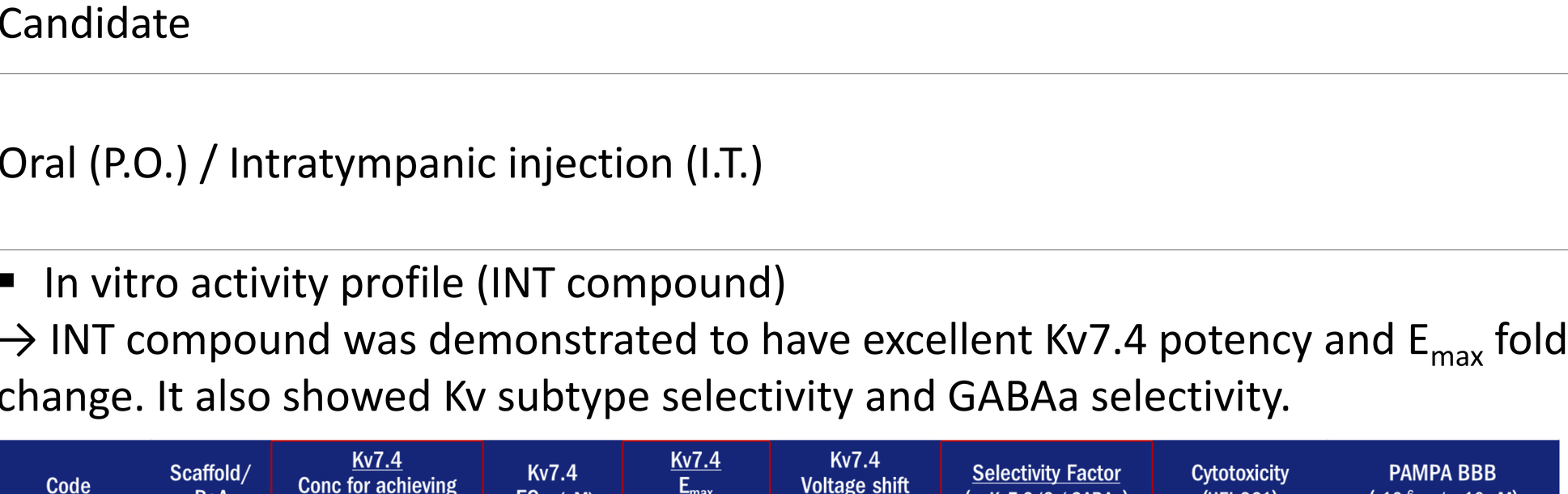
Development of a Kv7.4 selective activator for the treatment of sensorineural hearing loss (noise-induced, ototoxic, and hereditary)

iN Therapeutics

Disease Area	Others
Product Type	Small Molecule (Kv7.4 selective activator)
Indication	Sensorineural hearing loss (noise-induced, ototoxic, and hereditary)
Target	Kv7.4 (K+) channel
Mechanism of Action	Disruption of Kv7.4 channel function (excessive noise, ototoxic drug, Kv7.4 mutation) → Impaired K+ recycling →outer hair cell death → sensorineural hearing loss Kv7.4 selective activators protect against hearing loss by restoring K+ recycling in the inner ear
Competitiveness	Competitive drug development - ACOU-085 (Acousia Tx): Non-selective Kv7.4 activator, Phase I, I.T. formulation iNT Candidate, First-in-class Kv7.4 selective activator - Improved Kv7 subtype selectivity - Improved Kv7.4 potency & efficacy - Reduced risk of CNS side effects - A profile that can be developed as an oral & I.T. formulation drug
Development Stage	Candidate
Route of Administration	Oral (P.O.) / Intratympanic injection (I.T.)
Key Data	▪ In vitro activity profile (INT compound) → INT compound was demonstrated to have excellent Kv7.4 potency and E_{max} fold change. It also showed Kv subtype selectivity and GABAa selectivity.

Code	Scaffold/ RoA	Kv7.4 Conc for achieving 2-fold change (μM)	Kv7.4 EC_{50} (μM)	Kv7.4 E_{max} fold change	Kv7.4 Voltage shift ($\Delta V_{1/2}$,mV)	Selectivity Factor (vs Kv7.2/3 / GABAa)	Cytotoxicity (HEI-OC1)	PAMPA BBB ($x10^{-6}$cm/s, 10 μM)
INT Compound	A / P.O.	0.28	3.20	≒11	-20.4 mV	20.6 / ---	> 30 μM	8.41

▪ Noise induced hearing loss model (INT compound single injection before Noise)



→ INT compound exhibited a remarkable 40 dB hearing protection efficacy in an in vivo noise-induced hearing loss (NIHL) model, building upon its impressive in vitro profile.