

RESEARCH MONOGRAPH . COMPOUND PROFILE

Tesofensine

A triple reuptake inhibitor originally developed for Alzheimer's and Parkinson's disease and repurposed for obesity, advanced through Phase 2 with substantial body weight reduction relative to placebo.

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AUTHOR	Kodiac bioLabs Research
COMPOUND CLASS	Triple monoamine reuptake inhibitor (DA, NE, 5-HT)

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ABSTRACT

Tesofensine (NS2330; CAS 195875-84-4; molecular formula $C_{17}H_{23}Cl_2N$; molecular weight 312.28) is a triple monoamine reuptake inhibitor developed by NeuroSearch in the 1990s as a candidate for Alzheimer's disease and Parkinson's disease (where dopamine reuptake inhibition was hypothesized to provide motor symptom relief without the on-off fluctuations of L-DOPA). The compound failed to demonstrate efficacy in the original Alzheimer's and Parkinson's indications; weight loss observed as an adverse event in the central nervous system trials motivated repurposing for obesity, with Phase 2 data published in 2008 showing approximately 10 percent body weight reduction at 24 weeks at the 0.5 mg dose, substantially greater than the comparator orlistat and meaningfully greater than the GLP-1 agonist liraglutide at typical doses. Mechanism is competitive inhibition at the dopamine, norepinephrine, and serotonin transporters with similar affinity at all three sites; the integrated effect is monoamine elevation in mesolimbic, prefrontal, and hypothalamic targets that suppresses appetite and increases energy expenditure. The compound was advanced through Phase 3 by NeuroSearch and partner Saniona for obesity but Phase 3 enrollment was paused multiple times owing to safety signals (modest blood pressure elevation, dry mouth, insomnia, mood changes) and the program has progressed slowly relative to the more recent GLP-1 class. Saniona has continued development for hypothalamic obesity (Prader-Willi syndrome and acquired hypothalamic obesity from craniopharyngioma surgery), with the rationale that the central monoamine elevation may compensate for hypothalamic dysfunction in these niche populations. The

compound is not approved in any jurisdiction. Plasma half-life is approximately 9 days, suitable for once-daily oral administration with steady-state achieved over 4 weeks.

1. 1. Compound Identification

Tesofensine is described as triple monoamine reuptake inhibitor (da, ne, 5-ht). A triple reuptake inhibitor originally developed for Alzheimer's and Parkinson's disease and repurposed for obesity, advanced through Phase 2 with substantial body weight reduction relative to placebo.

1.1. 1.1 Class summary

Triple monoamine reuptake inhibitor (DA, NE, 5-HT)

1.2. 1.2 Subtitle

A triple reuptake inhibitor originally developed for Alzheimer's and Parkinson's disease and repurposed for obesity, advanced through Phase 2 with substantial body weight reduction relative to placebo.

2. 2. Abstract

Tesofensine (NS2330; CAS 195875-84-4; molecular formula C₁₇H₂₃Cl₂N; molecular weight 312.28) is a triple monoamine reuptake inhibitor developed by NeuroSearch in the 1990s as a candidate for Alzheimer's disease and Parkinson's disease (where dopamine reuptake inhibition was hypothesized to provide motor symptom relief without the on-off fluctuations of L-DOPA). The compound failed to demonstrate efficacy in the original Alzheimer's and Parkinson's indications; weight loss observed as an adverse event in the central nervous system trials motivated repurposing for obesity, with Phase 2 data published in 2008 showing approximately 10 percent body weight reduction at 24 weeks at the 0.5 mg dose, substantially greater than the comparator orlistat and meaningfully greater than the GLP-1 agonist liraglutide at typical doses. Mechanism is competitive inhibition at the dopamine, norepinephrine, and serotonin transporters with similar affinity at all three sites; the integrated effect is monoamine elevation in mesolimbic, prefrontal, and hypothalamic targets that suppresses appetite and increases energy expenditure. The compound was advanced through Phase 3 by NeuroSearch and partner Saniona for obesity but Phase 3 enrollment was paused multiple times owing to safety signals (modest blood pressure elevation, dry mouth, insomnia, mood changes) and the program has progressed slowly relative to the more recent GLP-1 class. Saniona has continued development for hypothalamic obesity (Prader-Willi syndrome and acquired hypothalamic obesity from craniopharyngioma surgery), with the rationale that the central monoamine elevation may compensate for hypothalamic dysfunction in these niche populations. The compound is not approved in any jurisdiction. Plasma half-life is approximately 9 days, suitable for once-daily oral administration with steady-state achieved over 4 weeks.

3. Mechanism of Action

Competitive inhibition at DAT, NET, and SERT with similar potency. Central monoamine elevation suppresses appetite (hypothalamic POMC and CART activation, dopaminergic mesolimbic modulation of food reward) and increases energy expenditure.

The mechanistic profile described above represents the consensus position from peer-reviewed literature where available; for compounds with sparse formal characterization, this section reflects vendor-grade reports and structurally-related class pharmacology and should be interpreted with appropriate caution.

4. 4. Pharmacokinetics and Routes of Administration

Pharmacokinetic data are summarized within the abstract for compounds with formal Phase 1 records. Compounds without published human pharmacokinetic studies are noted as such; investigators should treat the absence of data as a research limitation.

5. 5. Reported Research Dose Ranges

Phase 2 obesity 0.25 to 1 mg per oral administration once daily. Phase 3 hypothalamic obesity 0.25 to 0.5 mg.

Doses are scaled from clinical use where the compound is approved as a medicine, from Phase 2/3 trials where development advanced, or from rodent dose-response data scaled by allometric assumptions where the compound has no human clinical record. Investigators should treat dose ranges from research-chemical-grade vendors as starting points for their own pharmacokinetic and tolerability characterization rather than validated dosing recommendations.

6. Sourcing and Quality Verification

Investigators should obtain analytical confirmation of identity (mass spectrometry; for peptides, additionally amino acid analysis or N-terminal sequencing) and purity (HPLC area-percent, ideally greater than 95 percent) on every lot. Vendor certificates of analysis vary in quality; third-party analytical confirmation through independent laboratories (e.g., Janoshik Analytical, Anabolic Lab) is the gold standard for research-grade peptides and small molecules.

For compounds with established pharmaceutical-grade marketing in any jurisdiction, sourcing from the marketed product (where legal and accessible) provides the highest quality assurance.

7. 7. Reconstitution and Handling

Peptides should be reconstituted in bacteriostatic water or sterile water for injection in the volume appropriate to the desired concentration; lyophilized peptides should be allowed to come to room temperature before reconstitution to minimize precipitation. Reconstituted peptides should be stored refrigerated and used within the timeframe specified by the manufacturer (typically 14 to 30 days for bacteriostatic water reconstitutions, shorter for sterile water).

Small molecules: storage conditions vary by compound; consult the certificate of analysis for the specific product. Most are stable at room temperature in dry, dark conditions; oxidation-sensitive compounds (e.g., catecholamine precursors) require cool storage and protection from light.

8. 8. Stack Interaction Considerations

Investigators combining this compound with other research substances should consider receptor-level interactions (additive effects at shared targets), enzyme-level interactions (CYP-mediated drug-drug interactions where applicable), and pharmacodynamic interactions (additive sedation, additive serotonergic activity, additive hemodynamic effects).

The stack interaction section in published monographs of well-characterized compounds is necessarily incomplete for any specific combination; investigators should treat novel combinations with elevated caution and titrate gradually.

9. 9. References

1. Astrup A, et al. Effect of tesofensine on bodyweight loss, body composition, and quality of life in obese patients. Lancet 2008.
2. Sjodin A, et al. The effect of tesofensine on appetite. Int J Obes 2010.
3. Saniona AB. Phase 2 hypothalamic obesity results. Press release 2022.

This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. Compound class generalizations are noted where compound-specific data are sparse; investigators should weight the evidence accordingly.