

Insilico Begins Phase I Study of AI-Driven NLRP3 Inhibitor

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The first-in-human dosing of ISM8969 marks the first clinical milestone in Insilico's co-development collaboration with Hygtia Therapeutics.



Insilico Medicine has completed first-in-human dosing in the Phase I clinical study of ISM8969, an AI-driven small-molecule inhibitor of the NLRP3 inflammasome.

The milestone marks the first clinical achievement in Insilico's co-development collaboration with Hygtia Therapeutics. ISM8969 is being developed as an orally available, brain-penetrant therapy for chronic neuroinflammation and central nervous system disorders, including Parkinson's disease.

This is relevant because neuroinflammation is increasingly recognised as an important driver of neurodegenerative disease progression. The NLRP3 inflammasome plays a role in innate immune signalling, but excessive or chronic activation can trigger overproduction of pro-inflammatory cytokines, contributing to sustained inflammation, cell damage and neuronal dysfunction.

Developing NLRP3 inhibitors for CNS disease has been technically challenging. Many clinically advanced NLRP3 inhibitors are peripherally restricted, limiting their ability to access the central nervous system. Insilico is positioning ISM8969 as differentiated because it is designed to cross the blood-brain barrier and act in the target compartment.

The Phase I study is a single-centre, randomised, double-blind, placebo-controlled trial. It includes both single ascending dose and multiple ascending dose cohorts, evaluating safety, tolerability, pharmacokinetics and pharmacodynamics of orally administered ISM8969.

The study is being conducted in Australia and is expected to enrol 80 healthy participants and 20 obese adult participants at risk of cardiovascular disease. It will also collect cerebrospinal fluid samples to assess central nervous system penetration and characterise pharmacokinetic and pharmacodynamic behaviour in the target compartment.

The clinical design is important because CNS drug development often fails when preclinical signals do not translate into adequate brain exposure or target engagement. Cerebrospinal fluid sampling may help clarify whether ISM8969 reaches the central nervous system at therapeutically relevant levels.

Insilico said ISM8969 showed promising in vitro activity and safety, favourable in vivo pharmacokinetic and pharmacodynamic profiles, and efficacy against inflammation in multiple mouse disease models, including acute inflammatory and chronic disease models. The programme was nominated as a preclinical candidate in December 2024.

The molecule was developed using Insilico's Chemistry42 platform, which the company said was used to optimise the candidate for preclinical efficacy and permeability. The programme reflects Insilico's broader strategy of using generative AI and automation to shorten early-stage drug discovery.

Under the exclusive global strategic co-development collaboration with Hygtia Therapeutics, both parties hold a 50 per cent stake in the global rights and interests of the programme. Insilico is leading the IND submission and Phase I clinical trial, and remains eligible to receive up to \$66 million in upfront and milestone payments as the programme progresses.

The development is commercially relevant because AI-discovered assets increasingly need clinical proof points to validate the platform model. First-in-human dosing does not yet confirm therapeutic efficacy, but it moves ISM8969 from discovery-stage claims into clinical evaluation.

Adoption and future development will depend on Phase I safety, pharmacokinetics, pharmacodynamics, CNS penetration data and whether the candidate can show biological activity relevant to neurodegenerative disease. Later studies will need to address patient selection, disease stage, biomarkers and clinically meaningful outcomes.

The programme also reflects a broader shift in AI drug discovery. The industry is moving from platform announcements toward measurable clinical milestones. For Insilico, the key question is whether AI-generated candidates can produce not only faster preclinical timelines, but also differentiated clinical assets in difficult therapeutic areas such as neurodegeneration.