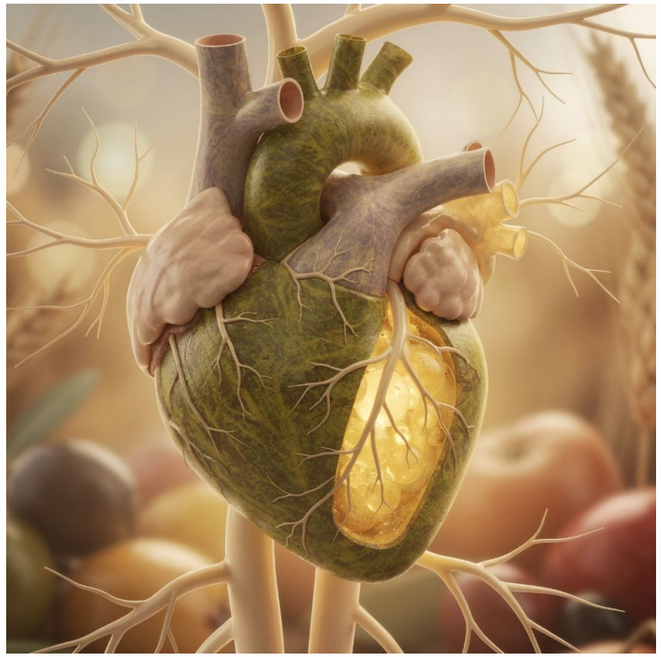
NB-008 – Best-in-Class Oral PCSK9 Inhibitor

Transforming cardiovascular and oncology treatment with the first oral small molecule PCSK9 inhibitor, delivering unmatched patient convenience and expanded access to life-saving therapy.

NAVIKA BIO

NB-008: Best-in-Class Oral PCSK9 Inhibitor



Oral Small Molecule Innovation

NB-008 is a best-in-class oral small molecule PCSK9 inhibitor for primary hyperlipidemia, familial hypercholesterolemia, cardiovascular disease and potentially oncology. This oral tablet addresses a **$6B market opportunity** currently dominated by injectable biologics.

The program is in IND-enabling studies with **strong global patent protection beyond 2041** (PCT filed). As the first oral small molecule PCSK9 inhibitor, NB-008 offers transformative advantages over existing injectable monoclonal antibodies.

Oral Bioavailability

Small molecule enables convenient oral dosing versus bi-weekly or monthly injections

Cost Advantage

Dramatically lower drug costs compared to biologics expand patient access and payor adoption

Patient Preference

Oral administration eliminates injection site reactions and improves treatment acceptance

ASCVD and Cholesterol Challenge

Global ASCVD Crisis

Atherosclerotic cardiovascular disease (ASCVD) remains a **primary cause of morbidity and mortality worldwide**, responsible for more deaths annually than any other cause. Despite significant advances in prevention and treatment over the past decades, ASCVD continues to impose an enormous burden on healthcare systems and patient quality of life.

Elevated low-density lipoprotein cholesterol (LDL-C) is recognized as **one of the major modifiable risk factors for ASCVD**. Extensive epidemiological and clinical trial evidence demonstrates a clear causal relationship between LDL-C levels and cardiovascular events. Each 39 mg/dL reduction in LDL-C correlates with approximately 20% reduction in major cardiovascular events.

Statin Limitations

Statins are the most commonly prescribed cholesterol-lowering drugs and have proven efficacy in reducing ASCVD events and lowering LDL-C levels. However, **statins face significant clinical limitations** that create substantial unmet medical need:

Adverse reactions: Abnormal liver function, myalgia (muscle pain affecting 10-15% of patients), myositis, and rare but serious rhabdomyolysis

Tolerance issues: Insufficient efficacy in high-risk patients and the "6% effect" - each doubling of statin dose yields only ~6% additional LDL-C reduction

Metabolic concerns: Increased risk of new-onset diabetes, particularly in predisposed populations

Drug interactions: CYP450 metabolism creates combination therapy challenges

> These significant limitations with statins have driven an urgent need for non-statin-based cholesterol-lowering drugs. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors represent a breakthrough cholesterol-lowering strategy, decreasing LDL-C levels by 50-60% through a complementary mechanism that enhances the liver's ability to clear LDL-C from circulation. However, current PCSK9 inhibitors are expensive injectable biologics, limiting patient access and adherence.

Clinical Limitations of Current Lipid-Lowering Therapies

Despite proven efficacy, existing lipid-lowering therapies face significant clinical challenges that limit their utility and create opportunities for innovation.

Statin Adverse Events

- Hepatotoxicity with elevated liver enzymes
- Myalgia, myositis, and rhabdomyolysis
- Increased diabetes risk in susceptible patients
- Drug-drug interactions

Statin Efficacy Limitations

"6% Rule": Each doubling of statin dose yields only 6% additional LDL-C reduction

- Tolerance and non-response in 10-15% of patients
- Insufficient LDL lowering for high-risk patients

Injectable PCSK9 Barriers

- Annual costs of $5,900-$6,200 limit access
- Injection requirement reduces adherence
- Healthcare visit burden
- Cold chain logistics complexity

> There remains a critical unmet need for oral, cost-effective therapies that can provide robust LDL-C lowering without the adverse event profile of statins or the inconvenience of injectables.

Scientific Rationale: The PCSK9 Pathway

Atherosclerotic cardiovascular disease (ASCVD) remains the **leading cause of global morbidity and mortality**, with elevated LDL cholesterol representing a primary modifiable risk factor. While statins have dominated lipid management for decades, their mechanism-based limitations and tolerability issues necessitate alternative approaches.

The PCSK9 Opportunity

Proprotein convertase subtilisin/kexin type 9 (PCSK9) emerged as a validated therapeutic target following genetic studies linking loss-of-function mutations to dramatically reduced cardiovascular risk. PCSK9 promotes degradation of hepatic LDL receptors; inhibiting PCSK9 increases receptor density and enhances LDL-C clearance.

Current PCSK9 inhibitors (monoclonal antibodies and siRNA) validate the target but suffer from administration challenges and cost barriers that limit widespread adoption. The market demands an oral solution.

Clinical Imperatives

- Hyperlipidemia affects over 95 million Americans
- Statin intolerance impacts 10-15% of patients
- Many high-risk patients fail to achieve guideline LDL targets
- Adherence to injectable therapies remains suboptimal

PCSK9 Market Landscape & Growth Trajectory

The PCSK9 inhibitor market demonstrates strong and accelerating growth, with total sales reaching $1.88B in 2022. Market expansion is driven by increasing cardiovascular disease prevalence, expanding indications, and improved reimbursement access.

9.3x

Evolocumab Growth

From $140M (2016) to $1.3B (2022)

4.3x

Alirocumab Growth

From $110M (2016) to $470M (2022)

$1.88B

Total Market 2022

Combined PCSK9 inhibitor sales

> Data Source: PHARMCUBE market intelligence. The market continues to expand as clinical evidence strengthens and reimbursement barriers diminish, creating significant opportunity for next-generation oral therapies.

Competitive Landscape: Oral PCSK9 Pipeline

The race to develop oral PCSK9 inhibitors involves multiple approaches, each with distinct advantages and liabilities. NB-008's **true small molecule design** positions it favorably against peptide- and alkaloid-based competitors.

Drug	Company	Mechanism	Status	Drug Type	Key Limitations
CVI-LM001	CVI Pharma	Reduces PCSK9 mRNA, stabilizes LDLR mRNA	Phase II	Alkaloid	High MW, poor bioavailability, toxicity concerns, difficult synthesis
NNC0385-0434	Novo Nordisk	Binds PCSK9, blocks LDL-R interaction	Phase II	Polypeptide	Poor oral bioavailability, formulation challenges
MK-0616	Merck	Binds PCSK9, blocks LDL-R interaction	Phase III	Cyclic Peptide	Limited bioavailability, complex formulation
AZD0780	AstraZeneca	Inhibits PCSK9-LDL-R binding	Phase II	Small Molecule	Mechanism details proprietary
DC371739	SIMM/Jiayue	Decreases PCSK9 expression, promotes LDLR	Phase I	Alkaloid	Alkaloid liabilities: toxicity, synthesis complexity
NB-008	**Navika Bio**	**Reduces PCSK9 mRNA**	**Preclinical**	**True Small Molecule**	**Best-in-class profile: high bioavailability, superior safety**

Alkaloid Challenges

High molecular weight compounds with poor bioavailability, elevated toxicity risk, complex synthesis, and high raw material costs limiting commercial viability.

Peptide Limitations

Polypeptides and cyclic peptides face inherent oral bioavailability challenges and require sophisticated formulation strategies to achieve adequate systemic exposure.

NB-008 Advantages

Optimized small molecule design delivers superior oral bioavailability (10-19% F), excellent safety profile, and scalable synthesis, overcoming limitations of competing approaches.

NB-008: Market Opportunity and Product Profile

Product Overview

Market Scale: $20B total addressable market

Indications: Primary hyperlipidemia, familial hypercholesterolemia, cardiovascular disease, oncology

Target: PCSK9 (proprotein convertase subtilisin/kexin type 9)

Development Stage: Preclinical (IND-enabling studies)

IP Protection: Strong global patent protection beyond 2041 (PCT filed)

NB-008 Key Highlights

- Oral small molecule with **low drug cost and convenient administration** versus injectable biologics
- Overcomes clinical limitations of statins with novel mechanism
- True small molecule design (not peptides/alkaloids in current clinical development)
- High safety profile and potent PCSK9 inhibition
- Two potential indications: lipid-lowering and anti-tumor

NB-008: Overcoming Statin Limitations with Dual Indications

Addressing Unmet Medical Needs

NB-008's oral small molecule approach delivers **significant advantages** over currently approved PCSK9 macromolecules, including substantially lower drug costs and convenient oral administration that transforms the patient experience. This accessibility advantage is particularly important for chronic cardiovascular disease management requiring lifelong therapy.

Overcomes Statin Limitations

Addresses statin intolerance, inadequate LDL reduction, and drug-drug interactions that limit current standard-of-care approaches. Provides alternative mechanism for patients who cannot achieve lipid goals with statins alone.

Competitive Differentiation

Current oral PCSK9 inhibitors in clinical development are limited to peptides and alkaloids with bioavailability challenges. NB-008's small molecule structure offers superior pharmaceutical properties and development advantages.

High Safety and Activity

Demonstrates excellent safety profile coupled with potent PCSK9 inhibition. Reduces PCSK9 mRNA levels, suggesting potential disease-modifying effects beyond current injectable biologics that only inhibit protein function.

Dual Indication Potential

Beyond cardiovascular disease, emerging evidence supports PCSK9's role in cancer biology, creating a **second major indication opportunity** in oncology. NB-008's oral formulation and safety profile make it particularly attractive for combination with cancer therapies, potentially opening entirely new therapeutic applications and market segments.

NB-008: High Activity, Bioavailability and Safety

NB-008 demonstrates an exceptional balance of **potency, pharmacokinetics and safety** that positions it as a differentiated oral PCSK9 inhibitor with compelling commercial potential.

Hypolipidemic Effect in Hamsters

NB-008 demonstrated **robust lipid-lowering activity** in the golden hamster model at 10 mg/kg oral dose:

Parameter	% Change
Triglycerides (TG)	**-71.8%**
Total Cholesterol	**-51.1%**
LDL-C	**-38.2%**
HDL-C	**+59%**

These results demonstrate potent efficacy across multiple lipid parameters, with particularly impressive reductions in atherogenic lipids and beneficial increases in protective HDL-C.

Pharmacokinetics in Rats

Parameter	IV (1 mg/kg)	PO Fasted	PO Fed
T½ (h)	11.1	12.3	10.6
Tmax (h)	-	3.33	9.33
Cmax (ng/mL)	-	268	379
AUC (h·ng/mL)	3,319	3,343	6,443
F (%)	-	**10.07**	**19.41**

Key findings: Extended half-life (10-12 hours) supports once-daily dosing. Food effect nearly doubles bioavailability to 19.4%, favorable for patient convenience.

Comprehensive Safety Profile

Assay	Result
hERG IC_{50}	>30 µM
Ames Test	**Negative**
CYP Inhibition	>30 µM (all isoforms)
CYP Induction	Minimal (CYP1A2 slight)
Liver Metabolites	84% parent compound
3-Week Rat NOAEL	**1,000 mg/kg/day**

Exceptional safety margins: No cardiac, genotoxic, or metabolic liabilities. Very high NOAEL provides substantial safety margin for clinical development.

NB-008: Pharmacological Activity - In Vitro and In Vivo

Potent PCSK9 Inhibition Across Multiple Models

NB-008 demonstrates **exceptional potency** in inhibiting PCSK9 both in cell-based assays and in animal models of hyperlipidemia. The compound's mechanism of action, reducing PCSK9 mRNA levels rather than just blocking protein function, represents a potentially **disease-modifying approach** that could provide more durable lipid-lowering effects than current injectable biologics.

92%

In Vitro Potency

PCSK9 inhibition in HepG2 cells at 10 µM concentration.

-59%

Hepatic PCSK9 mRNA

Reduction in liver PCSK9 expression in C57BL/6J mice.

-26%

LDL-C Reduction

Decrease in LDL cholesterol levels in C57BL/6J mice.

-72%

Triglyceride Reduction

Significant decrease in hamsters, exceeding typical statin performance.

In Vitro Activity

NB-008 was evaluated in HepG2 human hepatocellular carcinoma cells, a standard model for assessing hepatic PCSK9 regulation. At 10 µM concentration, NB-008 achieved **92% inhibition of PCSK9 levels** as measured by ELISA, demonstrating exceptional cellular potency.

This high level of inhibition suggests that NB-008 can effectively modulate PCSK9 expression in human hepatocytes, the primary site of PCSK9 production and LDL receptor regulation.

C57BL/6J Mouse Model

In the widely used C57BL/6J mouse model, NB-008 at 50 mg/kg oral dose produced a **58.7% reduction in hepatic PCSK9 mRNA expression**, directly confirming its mechanism of action at the transcriptional level.

This profound effect on PCSK9 mRNA translated to a **25.8% reduction in LDL-C levels**, demonstrating clear linkage between target engagement and pharmacological effect. The magnitude of LDL-C lowering is particularly impressive given the relatively resistant lipid profile of this mouse strain.

Hamster Model: Translational Relevance

The golden hamster model is highly predictive of human lipid metabolism. NB-008 at just 10 mg/kg achieved remarkable multi-parameter lipid improvements, including a **71.8% triglyceride reduction, 51.1% total cholesterol lowering, and 38.2% LDL-C decrease**. Additionally, it beneficially **increased HDL-C by 59%**. These results highlight NB-008's potential to match or exceed the lipid-modifying effects of high-dose statins, with the added benefit of oral administration.

NB-008: Pharmacokinetics - Optimized for Oral Delivery

NB-008 exhibits **exceptional oral bioavailability** for a small molecule PCSK9 inhibitor, with favorable half-life supporting once-daily dosing.

1

Superior Metabolic Stability

Human liver microsomes: 94 minutes half-life

Rat liver microsomes: 153 minutes half-life

Excellent metabolic stability predicts low clearance and sustained exposure in humans.

2

Bioavailability Excellence

Rat (fasting): 10% oral bioavailability

Rat (fed): 19.4% oral bioavailability

Hamster (fed): 307% relative bioavailability vs. fasting—demonstrates dramatic food enhancement effect.

3

Optimal Half-Life

Rat IV: 11.1 hours terminal half-life

Rat PO: 10.6-13 hours terminal half-life

Extended half-life supports convenient QD dosing regimen for patient compliance.

Rat Pharmacokinetic Parameters

Route/Condition	T1/2 (h)	Tmax (h)	Cmax (ng/mL)	AUC0-∞ (h·ng/mL)	F (%)
IV (1 mg/kg)	11.1	—	—	3,319	—
PO Fasting (10 mg/kg)	12.3	3.33	268	3,343	10.07
PO Fed (10 mg/kg)	10.6	9.33	379	6,443	19.41

> The food-enhanced bioavailability and extended half-life of NB-008 compare favorably to competing oral PCSK9 candidates, many of which struggle with single-digit bioavailability or require complex formulation strategies.

NB-008: DMPK Profile: Metabolic Stability and Bioavailability

Favorable Metabolic Stability and Oral Bioavailability

NB-008 exhibits an excellent DMPK profile, characterized by **favorable metabolic stability** and promising bioavailability, which supports its development as an orally-administered therapeutic.

Metabolic Stability & Bioavailability

NB-008 demonstrates **excellent metabolic stability** in liver microsomes, indicating low clearance and potential for once-daily dosing:

Human Liver Microsomes: T½ of **94.08 minutes**

Rat Liver Microsomes: T½ of **153.28 minutes**

These extended half-lives predict favorable human pharmacokinetic properties. In hamsters, NB-008 achieved a fasted bioavailability of **7.32%** with sustained absorption (Tmax = 16h), suggesting potential for **modified-release formulations** to optimize delivery.

Significant Food Effect on Bioavailability

A critical finding is the **substantial positive food effect** on NB-008 bioavailability in hamsters. Administration with food dramatically increased exposure, suggesting patients should take NB-008 with meals for optimal efficacy.

Dietary Status	AUC (ng·h/mL)	F (%)	Fold Increase (AUC)
Fasting	5,199	307.46	-
Fed	15,985	**946%**	**3.1×**

The fed state **increased AUC by 3.1-fold and Cmax by 2.7-fold**, while also shortening Tmax from 18.67 to 5.33 hours. This indicates faster and more complete absorption, which simplifies clinical development and improves patient compliance by allowing administration with meals.

NB-008: DMPK - Detailed Rat Pharmacokinetics

Comprehensive PK Assessment in Rats

Detailed pharmacokinetic studies in Sprague-Dawley rats evaluated the impact of **diet and formulation on NB-008 bioavailability**. These studies provide critical insights for formulation development and clinical dosing strategies, demonstrating that both fed state and improved solubilization can significantly enhance oral absorption.

Key findings from the rat studies illustrate the progression of NB-008's bioavailability under different conditions:

1

Fasted State Baseline

CMC-Na formulation in fasted rats achieved **10.07% bioavailability**, establishing baseline absorption.

2

Food Effect

The same formulation with food resulted in **16.66% bioavailability**, a 65% increase demonstrating a positive food effect.

3

Optimized Formulation

Using HP-β-CD solubilizer with food achieved **19.41% bioavailability**, nearly doubling baseline absorption.

Key Insights for Clinical Development

Extended Half-Life

A consistent T½ of 10-13 hours supports **once-daily dosing**, enhancing convenience and adherence.

Moderate Clearance

Favorable clearance and volume of distribution suggest good **tissue distribution** and safety for chronic dosing.

Formulation Strategy

The HP-β-CD formulation's high bioavailability with food provides a clear path for **optimizing clinical formulation**.

NB-008: Metabolite Profiling: Clean Metabolic Pathway

Clean Metabolic Profile with Minimal Metabolites

Metabolite identification studies in human, dog, and rat liver microsomes revealed that NB-008 has a **remarkably clean metabolic profile**. The parent compound represents **80-86% of the total peak** area across all three species, indicating low metabolic turnover and suggesting minimal formation of potentially active or toxic metabolites. Summary of key metabolites identified and their percentages across species:

Metabolite ID	Formula Change	Human (%)	Dog (%)	Rat (%)
Met-1	M+3O	-	0.4	-
Met-2	M+O+Glu	6.6	-	8.8
Met-3	M+2O	-	0.4	-
Met-4	M+O	1.1	9.7	0.6
Met-5	M+O	8.1	7.1	4.4
Met-6	M+O+2H	-	1.5	-
NB-008 (Parent)	M	**84.2**	**80.9**	**86.2**

Species-Specific Metabolic Profiles

Human Liver Microsomes

84.2% parent compound with only two minor metabolites detected: Met-2 (glucuronide conjugate, 6.6%) and Met-5 (mono-oxygenation, 8.1%). The predominance of parent drug suggests low hepatic extraction.

Dog Liver Microsomes

80.9% parent compound with the most diverse metabolite profile among tested species. Met-4 and Met-5 (both mono-oxygenated) represent 9.7% and 7.1% respectively, indicating modest Phase I metabolism.

Rat Liver Microsomes

86.2% parent compound, the highest proportion across species. Met-2 (glucuronide, 8.8%) is the major metabolite with minimal oxidative metabolism, supporting the excellent PK observed in rat efficacy studies.

> This consistent, clean metabolic profile across species indicates minimal metabolic liability for NB-008. It reduces the risk of metabolite-related toxicity and complex drug-drug interactions, simplifying regulatory discussions and enhancing the predictability of clinical outcomes. The identified metabolites are primarily simple, well-characterized oxidation and glucuronide conjugates, supporting a favorable safety profile.

NB-008: DMPK: Cytochrome P450 Inhibition Profile

Minimal Drug-Drug Interaction Risk

NB-008 was evaluated for its potential to inhibit major cytochrome P450 enzymes. Across all eight tested CYP isoforms, NB-008 showed **IC_{50} values >30 µM**, indicating negligible inhibition and a minimal risk of drug-drug interactions.

Broad Spectrum Safety

NB-008 demonstrated negligible inhibition across all 8 major CYP isoforms (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4-M, 3A4-T), with IC_{50} values consistently above 30 µM.

High Therapeutic Window

These IC_{50} values are far above anticipated therapeutic concentrations, indicating minimal risk of drug-drug interactions at clinically relevant doses.

Clinical Significance

The IC_{50} values >30 µM for all CYP isoforms are **far above anticipated therapeutic concentrations**, suggesting negligible potential for perpetrator drug-drug interactions. This is particularly important for a cardiovascular drug, as many patients will be on multiple concomitant medications.

The absence of CYP3A4 inhibition is especially notable, as this isoform metabolizes approximately 50% of all marketed drugs. Similarly, the lack of CYP2D6 and CYP2C9 inhibition reduces concerns about interactions with common cardiovascular medications.

Competitive Advantage

This clean CYP profile **differentiates NB-008 from many statins**, which often inhibit CYP3A4 and create significant drug-drug interaction concerns. The lack of CYP inhibition simplifies clinical development, reduces contraindications, and expands the patient population that can safely receive NB-008.

For patients with complex medication regimens, common in cardiovascular disease populations, NB-008's minimal DDI risk represents a substantial clinical advantage and reduces the need for dose adjustments or therapeutic drug monitoring.

NB-008: Drug Interaction Profile: Minimal CYP Liability

CYP Inhibition Panel: No Inhibition Detected

Comprehensive cytochrome P450 studies demonstrate that NB-008 exhibits **no significant inhibition** or induction of major drug-metabolizing enzymes, reducing risk of clinically significant drug-drug interactions.

CYP Isoform	NB-008 IC50 (μM)	Positive Control IC50 (μM)	Risk Assessment
CYP1A2	>30	1.83 (Furafylline)	No inhibition
CYP2B6	>30	3.80 (Ketoconazole)	No inhibition
CYP2C8	>30	3.75 (Quercetin)	No inhibition
CYP2C9	>30	0.30 (Sulfaphenazole)	No inhibition
CYP2C19	>30	6.84 (Tranylcypromine)	No inhibition
CYP2D6	>30	0.057 (Quinidine)	No inhibition
CYP3A4-M	>30	0.026 (Ketoconazole)	No inhibition
CYP3A4-T	>30	0.024 (Ketoconazole)	No inhibition

> **Clinical Significance**: IC50 values >30 μM across all major CYP isoforms indicate negligible potential for drug-drug interactions through inhibition of hepatic metabolism. This clean profile supports co-administration with commonly prescribed cardiovascular medications including statins, antihypertensives, and antiplatelet agents.

NB-008: DMPK: CYP Enzyme Induction – Enzymatic Activity

No Clinically Relevant Enzyme Induction

NB-008 was evaluated for its potential to induce CYP1A2, CYP2B6, and CYP3A4 enzyme activity in cultured human hepatocytes. Enzyme induction can lead to decreased exposure of co-administered drugs, representing another mechanism of drug-drug interactions. **NB-008 showed no meaningful induction of enzyme activity** for any of the three tested isoforms at concentrations up to 10 µM.

1

CYP1A2 Activity

At therapeutically relevant concentrations (≤1 µM), NB-008 showed **no CYP1A2 induction**, with 0.0% of the positive control response. Even at 10 µM, it was only 22.7% of the positive control.

2

CYP2B6 Activity

NB-008 showed **no CYP2B6 induction** at any concentration tested. At 10 µM, activity was only 0.3% of the positive control, and 0.7% at 1 µM.

3

CYP3A4 Activity

NB-008 demonstrated **no CYP3A4 induction**, with 0.0% of the positive control response even at supratherapeutic concentrations up to 10 µM.

Conclusion: No Potential for Induction-Based Drug-Drug Interactions

> The enzymatic activity assays demonstrate that NB-008 has **no potential to induce CYP1A2, CYP2B6, or CYP3A4** at clinically relevant concentrations. All results showed <1% or 0% of the positive control response, well below the FDA threshold of 20% relative induction that would trigger further clinical DDI studies. This clean induction profile, combined with the lack of CYP inhibition, indicates **minimal risk for either perpetrator or victim drug-drug interactions**, substantially simplifying clinical development and prescribing.

NB-008: DMPK: CYP Enzyme Induction – mRNA Expression

Minimal Transcriptional Induction

To complement the enzyme activity assays, NB-008 was evaluated for its effects on CYP mRNA expression levels using quantitative PCR in human hepatocytes. This more sensitive method can detect transcriptional changes that may not yet manifest as increased enzyme activity. The results confirm **minimal induction potential**, with only slight CYP1A2 mRNA elevation at the highest concentration tested.

1

CYP1A2 mRNA

At 10 µM, NB-008 showed 4.56-fold induction, representing **16.1% of the positive control** (Omeprazole). At therapeutic concentrations (≤1 µM), induction was negligible (<4% of positive control).

2

CYP2B6 mRNA

NB-008 demonstrated 1.80-fold induction at 10 µM, which is **7.15% of the positive control** (Phenobarbital). This indicates no meaningful induction at any tested concentration.

3

CYP3A4 mRNA

NB-008 showed **no significant CYP3A4 mRNA induction**, with values at or below vehicle control, and **0.0% of the positive control** (Phenobarbital) at 10 µM.

Overall CYP1A2 Assessment

The slight CYP1A2 mRNA induction (16.1% of positive control) seen at a supratherapeutic concentration (10 µM) is **unlikely to be clinically significant**, as induction was negligible at 1 µM and below.

Overall CYP2B6 & CYP3A4 Assessment

For both CYP2B6 and CYP3A4, NB-008 showed **no meaningful mRNA induction** at any concentration tested, with all results <8% of positive control responses. The lack of CYP3A4 induction is particularly important given this isoform's dominant role in drug metabolism.

Conclusion: Minimal Induction Risk. The mRNA expression data confirm that NB-008 could potentially induce CYP1A2 mRNA expression at high concentrations, but this effect is weak (16% of positive control) and unlikely to translate to clinically significant enzyme induction. For CYP2B6 and CYP3A4, there is **no induction concern**. Overall, these results support a **low risk of induction-based drug-drug interactions** in clinical use, consistent with the enzyme activity data and reinforcing NB-008's favorable DDI profile.

NB-008: CYP Induction Studies: Minimal Induction Risk

Human hepatocyte induction studies reveal **no clinically relevant enzyme induction**, with only modest CYP1A2 mRNA elevation that does not translate to enzymatic activity changes.

Enzyme Activity Assessment

CYP	Compound (Conc.)	Activity %	Conclusion
1A2	Vehicle	100	No induction
1A2	NB-008 (10 µM)	229	
1A2	Omeprazole	667	Positive control
2B6	NB-008 (10 µM)	102	No induction
3A4	NB-008 (10 µM)	8.6	No induction

Result: No potential for enzyme induction across CYP1A2, CYP2B6, and CYP3A4 based on activity assays.

mRNA Expression Analysis

CYP	Compound	Fold Change	% of Control
1A2	NB-008 (10 µM)	4.56	16.1%
1A2	Omeprazole	23.1	100%
2B6	NB-008 (10 µM)	1.80	7.2%
3A4	NB-008 (10 µM)	0.85	0%

Note: Modest CYP1A2 mRNA elevation (4.56-fold) represents 16% of positive control response and does not translate to increased enzymatic activity, indicating no clinically relevant induction.

> NB-008 demonstrates a favorable drug interaction profile with no CYP inhibition and minimal, non-clinically significant induction potential. This profile supports combination therapy with standard-of-care cardiovascular medications.

NB-008: Safety Profile: Cardiac Safety and Genotoxicity

Comprehensive Safety De-Risking

NB-008 has been evaluated in standard safety pharmacology assays to assess two critical liabilities: **cardiac ion channel effects** (hERG) and **genotoxic potential** (Ames test). Both assays returned favorable results, substantially de-risking the clinical development program and supporting NB-008's potential as a chronic therapy for cardiovascular disease.

hERG Channel Safety

The human ether-à-go-go-related gene (hERG) potassium channel is critical for cardiac repolarization. Inhibition of hERG can lead to QT prolongation and potentially fatal arrhythmias (Torsades de Pointes), representing a major cause of drug withdrawals and development failures.

Compound	Top Concentration Tested	hERG IC_{50}
NB-008	30 µM	**>30 µM**

NB-008 showed **no hERG inhibition at concentrations up to 30 µM**, far exceeding anticipated therapeutic exposure levels. This IC_{50} >30 µM provides an excellent safety margin (typically >30-fold above therapeutic Cmax) and indicates **minimal cardiac liability**. This clean hERG profile is particularly important for a cardiovascular drug where patient populations may have pre-existing cardiac conduction abnormalities.

Ames Genotoxicity Assessment

The Ames bacterial reverse mutation test is the gold standard screening assay for mutagenic potential. A positive result would indicate DNA-damaging effects and raise serious concerns about carcinogenic potential, potentially precluding chronic use.

Result: NEGATIVE

NB-008 tested **negative in the Ames assay** across a broad concentration range (1.5-1000 µg/well) in multiple Salmonella typhimurium strains with and without metabolic activation. This negative result indicates:

No mutagenic potential through direct DNA interaction

No metabolic activation to mutagenic species

- Strong support for chronic dosing safety
- Reduced regulatory concerns around carcinogenicity studies

The negative Ames result is particularly reassuring given the intended chronic use in cardiovascular disease prevention, where patients may be treated for decades.

>30

hERG Safety Margin

Fold-margin above expected therapeutic concentrations, indicating negligible cardiac risk.

0

Mutagenic Signals

No mutagenic activity detected in comprehensive Ames testing, supporting chronic use safety.

1000

NOAEL (mg/kg/day)

No observed adverse effect level in 3-week rat toxicology study, providing substantial safety margins.

NB-008: Safety: 3-Week Repeated Dose Toxicology Study

Study Objective and Design

A comprehensive **3-week repeated dose toxicology study** was conducted in Sprague-Dawley rats to evaluate the safety profile of NB-008 following oral administration. This GLP-compliant study aimed to characterize toxic reactions, establish dose-response relationships, and determine the no observed adverse effect level (NOAEL) to support IND-enabling activities and inform first-in-human dose selection.

Rationale for Dose Selection

Efficacy data: 10-50 mg/kg showed robust lipid-lowering effects in animal models.
Preliminary toxicity: No adverse effects observed in shorter-duration range-finding studies.
Multiples of human equivalent dose: Doses provide substantial multiples (>100×) of anticipated human therapeutic exposure.

Regulatory guidance: High dose selected to achieve toxicity or maximum feasible dose (1,000 mg/kg).

Study Objectives

Toxicity characterization: Identify target organs and toxic manifestations.

Severity assessment: Determine nature and severity of adverse effects.

Dose-response: Establish relationships between dose and toxic effects.

NOAEL determination: Define highest dose with no adverse effects.

Safety margins: Calculate multiples for human dose selection.

Reversibility: Assess potential for recovery (through histopathology).

Study Groups

4 groups: vehicle control and 3 NB-008 dose groups (20 male, 20 female SD rats).

Dose Levels

Low (100 mg/kg), medium (300 mg/kg), high (1,000 mg/kg) orally once daily for 21 days.

Administration

Gavage dosing at 10 mL/kg volume with 0.5% CMC-Na as vehicle.

Monitoring

Daily clinical observations, weekly body weights/food, ophthalmoscopy, clinical pathology, organ weights, histopathology.

NB-008: Safety - 3 Week Toxicology Results (Part 1)

No Treatment-Related Adverse Effects Observed

Throughout the 3-week study period, comprehensive monitoring revealed **no treatment-related adverse effects** at any dose level up to and including 1,000 mg/kg/day. All assessed parameters remained within normal ranges, demonstrating NB-008's excellent tolerability in a repeat-dose setting.

Clinical Observations

No abnormalities in appearance, behavior, or activity. Animals remained healthy.

Body Weights

Normal growth curves maintained, no significant differences from controls.

Food Consumption

Normal feeding behavior and appetite, no palatability issues.

Ophthalmoscopy

Clear ocular examinations; no treatment-related changes observed.

Hematology Parameters

Complete blood counts showed **no time-effect or dose-effect correlation changes**. All values remained within normal reference ranges, with no trends suggesting hematologic toxicity. This is particularly important given the potential for some lipid-lowering agents to affect blood cell production or function.

Coagulation Studies

Coagulation parameters showed **no time-effect or dose-effect correlation changes**. Normal hemostatic function was maintained, indicating no adverse effects on the coagulation cascade. This finding is reassuring for a cardiovascular drug that may be co-administered with antiplatelet or anticoagulant therapies.

NB-008: Safety - 3 Week Toxicology Results (Part 2)

Comprehensive Clinical Pathology Evaluation

Extensive clinical pathology assessments revealed **minimal findings of no toxicological significance**. Observations were sporadic, not dose-dependent, and within normal biological variation.

Clinical Chemistry

No hepatic or renal toxicity. All values within normal ranges, indicating no hepatotoxicity or nephrotoxicity.

Urinalysis

Normal renal function maintained. No obvious regular changes related to test article administration.

Organ Weights

A **slight increase in spleen weight** was noted, but it:

- Showed no clear dose-response
- Was not associated with microscopic changes
- Fell within normal biological variation
- Was not accompanied by clinical signs

No other organs showed treatment-related weight changes, indicating **no target organ toxicity**.

Gross Pathology

Necropsy revealed two sporadic findings in the low-dose group:

One female (2116): **Yellow-white nodule** in liver—likely incidental.

One female (2118): **Dark red change** in eye—likely minor hemorrhage.

These isolated findings, with **no similar observations at higher doses**, are considered incidental and not treatment-related.

Accelerating Innovation to Improve Patients' Lives

Navika Bio bridges East and West, connecting groundbreaking Asian biotech innovation with global pharmaceutical partners to deliver transformative therapies to patients worldwide.

NAVIKA BIO

Let's Connect

For more information about partnership opportunities and to join us on this exciting journey of bringing transformative therapies to patents worldwide, please reach out to:

Lawrence Hu, PhD

Chief Technology Officer
Head of Business Development

Phone: 973-967-9949

Email: lawrence@navikabio.com