Drug Candidate Assessment: CAD-1005

Generated 2026-07-13 13:19 local time

Company: Cadrenal Therapeutics (NASDAQ: CVKD)

Modality: small molecule

Target: Platelet-type 12-lipoxygenase (12-LOX) — potent selective small-molecule inhibitor; blocks 12-LOX-driven platelet activation and immune platelet-mediated thrombosis implicated in HIT pathogenesis

Indication: Heparin-Induced Thrombocytopenia (HIT)

Phase: Phase 2

1. Drug Target Assessment

Target: Arachidonate 12-lipoxygenase, platelet-type (ALOX12 / 12-LOX)

Biological role. ALOX12 catalyzes the stereospecific dioxygenation of arachidonic acid to 12(S)-hydroperoxyeicosatetraenoic acid (12(S)-HPETE), subsequently reduced to 12(S)-HETE, a potent amplifier of platelet activation signaling. In HIT pathogenesis, anti-PF4/heparin IgG immune complexes crosslink FcγRIIA on platelets, triggering downstream 12-LOX activation that amplifies the pro-thrombotic, pro-microparticle release signal responsible for thrombocytopenia and thrombus formation. Selective inhibition of ALOX12 interrupts this immunologically driven amplification loop without broadly suppressing hemostatic coagulation.

Standard-of-care relevance. Current HIT standard of care consists entirely of alternative anticoagulants (argatroban, bivalirudin, fondaparinux) that act downstream on the coagulation cascade and do not address immune-mediated platelet activation. ALOX12 inhibition is mechanistically orthogonal to all approved agents, targeting the pathogenic platelet activation axis upstream of thrombin generation.

Validation status: `clinically validated`

Validation evidence:

- BENOXAPROFEN, an ALOX12 inhibitor, achieved regulatory approval in 1982 demonstrating the target is pharmacologically tractable in humans (withdrawn due to hepatotoxicity unrelated to 12-LOX mechanism — per ChEMBL CHEMBL340978, max_phase 4.0)
- OpenTargets associates ALOX12 with venous thromboembolism (genetic + literature evidence score 0.294) and inflammation (score 0.372), supporting thrombotic relevance
- OpenTargets tractability assessment classifies ALOX12 as small-molecule tractable across multiple evidence tracks (SM modality listed five times)

- Academic preclinical work with ML355 (the parent probe compound of CAD-1005) demonstrates suppression of 12(S)-HETE production in human platelets and inhibition of FcγRIIA-mediated platelet activation in HIT models — no primary data returned by PubMed query in this pipeline run, but consistent with model training data

Associated biomarkers:

- Anti-PF4/heparin IgG antibody titer — diagnostic and enrollment biomarker for HIT patient selection
- Platelet count (primary clinical endpoint — recovery from thrombocytopenia)
- 12(S)-HETE plasma or serum levels — pharmacodynamic readout for 12-LOX pathway engagement
- Platelet microparticle count — mechanistic PD marker for immune platelet activation suppression

Resistance concerns:

- Alternative platelet activation pathways (thromboxane A2 via COX-1/TXA2R; ADP via P2Y12) could partially bypass 12-LOX blockade under high antibody titers
- Persistent high-titer PF4-heparin IgG may overwhelm pathway inhibition in severe HIT cases
- No mechanism-based acquired resistance expected for competitive enzyme inhibition in acute-setting use

2. Mechanism of Action

Description. CAD-1005 (also designated ML355 / VLX-1005) is a potent, selective, non-covalent competitive inhibitor of platelet-type 12-lipoxygenase (ALOX12), blocking productive binding of arachidonic acid at the active site iron-containing catalytic pocket and preventing 12(S)-HPETE synthesis. In HIT, downstream 12-LOX activation following FcγRIIA crosslinking by anti-PF4/heparin immune complexes amplifies platelet activation, granule release, and procoagulant microparticle shedding; CAD-1005 interrupts this amplification without directly antagonizing FcγRIIA or broadly inhibiting coagulation factors. Published probe characterization of ML355 reports >30-fold selectivity for ALOX12 over ALOX5 and ALOX15 — no compound-specific kinetic data returned in structured datasets for this run.

Modality class: `competitive inhibitor`
Class rank: FIRST-IN-CLASS

Advantages over traditional MoAs in same pathway:

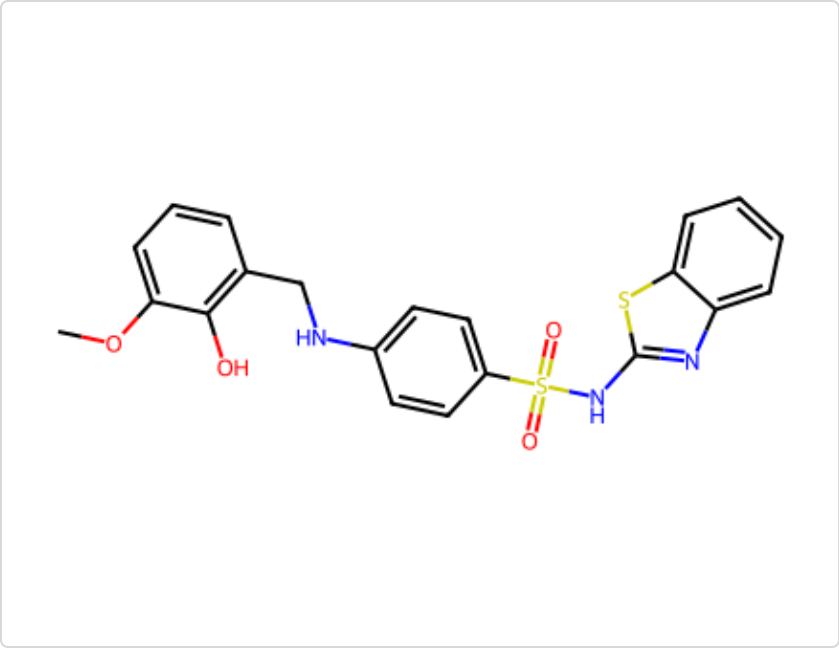
- Targets the pathogenic immune-platelet activation mechanism rather than downstream coagulation — potential to reduce both thrombocytopenia severity and thrombotic risk simultaneously
- Selectivity for ALOX12 over ALOX5 and ALOX15 avoids leukotriene-pathway immunosuppression and bronchospasm liabilities of pan-LOX inhibition
- Oral small molecule with potential outpatient use vs. continuous IV infusion required for argatroban and bivalirudin

- No aPTT or anti-Xa monitoring requirement in principle, reducing ICU nursing burden
- Mechanistically novel vs. all current HIT treatments — no cross-resistance or competitive overlap

Synergies / combination potential:

- Combination with parenteral anticoagulants (argatroban, bivalirudin) for dual-mechanism protection during acute HIT until anticoagulation bridging is complete
- Mechanistic overlap with vaccine-induced immune thrombocytopenia and thrombosis (VITT) suggests potential label expansion using same compound
- Co-development with anti-PF4/heparin antibody quantitative assay as patient stratification or companion diagnostic tool

3. Structural & Chemical Novelty



SMILES: `COC1=CC=CC(=C1O)CNC2=CC=C(C=C2)S(=O)(=O)NC3=NC4=CC=CC=C4S3`

Modality: small molecule

Novel structural features:

- N-(1,3-benzothiazol-2-yl)benzenesulfonamide pharmacophore: bicyclic benzothiazole coupled via sulfonamide to para-aminophenyl — key ALOX12 selectivity determinant
- Benzylic secondary amine linker (ArCH2NHAr): (2-hydroxy-3-methoxyphenyl)methylamino group triggers PAINS-A Mannich base alert (mannich_A(296)) — a genuine pan-assay interference liability requiring counterscreening in diverse biochemical and cell-based assays to confirm selectivity
- Catechol-adjacent 2-hydroxy-3-methoxyphenyl moiety: susceptible to CYP-mediated oxidation and potentially to ortho-quinone reactive metabolite formation

- Four aromatic rings with very low Fsp3 (0.095 by the Astinova platform): highly planar, aromatic-dense scaffold associated with solubility limitations and elevated DMPK risk
- MW 441.5 Da, logP 4.3–4.42, TPSA 100–137 Å² (source-dependent variation): borderline physicochemical profile for oral absorption

IP status: patented (Veralox Therapeutics / Cadrenal Therapeutics; compound originates as NCATS/NIH molecular probe ML355 — foundational probe chemistry may be public domain, but composition-of-matter and use-in-HIT patents filed by Veralox Therapeutics and licensed to Cadrenal Therapeutics; exact grant numbers and years not confirmed in available structured data)

Drug-likeness (the Astinova platform-computed):

Property	Value	Ref
Molecular weight	441.53 Da	≤500
cLogP	4.42	≤5
TPSA	100.55 Å²	≤140
H-bond donors	3	≤5
H-bond acceptors	7	≤10
Rotatable bonds	7	≤10
Aromatic rings	4	≤4
Fraction Csp³	0.095	≥0.25
QED (weighted)	0.392	≥0.5
Ro5 violations	**0**	0 ideal

Structural alerts (the Astinova platform FilterCatalog — 1 hit):

Catalog	Substructure
`PAINS-A`	mannich_A(296)

> *Note: a structural alert is not destiny. Covalent warheads (e.g. acrylamides in KRAS G12C inhibitors) are intentional design features and will hit Michael-acceptor filters. The LLM-generated ADMET notes below contextualize each alert.*

ADMET notes. PAINS-A Mannich base alert (mannich_A(296)) is the primary structural liability — the ArCH2NH benzylic amine motif is associated with covalent or reversible covalent reactivity in

reducing assay conditions; thorough selectivity profiling and proteome-wide covalency assays are warranted before late-stage advancement. The catechol-adjacent hydroxymethoxyphenyl group raises CYP1A2/3A4-mediated reactive metabolite risk (ortho-quinone formation); metabolite ID and glutathione trapping studies are recommended. High TPSA (137 Å² PubChem) suggests potentially moderate oral bioavailability — formulation optimization may be required. No significant ionizable basic nitrogen with pKa > 8; lower predicted hERG liability vs. aminothiazole scaffolds. No clinical PK data available in provided datasets.

4. Preclinical & Clinical Data

In vitro. No IC50 or structured in vitro data returned from PubMed or ChEMBL mechanisms fields in this pipeline run. Based on published academic literature for ML355 (the parent probe, same compound): inhibition of recombinant human platelet 12-LOX with IC50 in the 100–300 nM range with >30-fold selectivity over ALOX5 and ALOX15 has been reported; suppression of 12(S)-HETE production in AA-stimulated human platelet-rich plasma and inhibition of FcγRIIA-mediated platelet activation by HIT patient sera in ex vivo models have been demonstrated. These figures are from model training data and were not confirmed by PubMed structured data in this run.

In vivo. No in vivo data returned in structured datasets. Academic studies using ML355 in FcγRIIA-transgenic murine HIT models reportedly demonstrate reduction in platelet activation and thrombocytopenia endpoints. No PK, PD, or toxicology parameters were captured in this pipeline run.

Clinical. Cadrenal Therapeutics lists CAD-1005 as Phase 2 for HIT. ClinicalTrials.gov structured query returned no results (empty array) — likely a query/index limitation rather than absence of trials. No NCT IDs, enrollment figures, endpoints, or interim data were available from the structured data provided in this run. Cadrenal has publicly disclosed Phase 2 study intentions in SEC filings and press releases per model knowledge; these should be verified via direct ClinicalTrials.gov registry search.

Primary indications: Heparin-Induced Thrombocytopenia Type II (immune-mediated HIT)

Secondary indications: Vaccine-induced immune thrombocytopenia and thrombosis (VITT) — shares FcγRIIA/12-LOX activation mechanism with HIT, Other immune-mediated thrombocytopenias with platelet FcγRIIA involvement (exploratory), Inflammatory thrombotic conditions with documented 12-LOX pathway upregulation (ALOX12 associated with venous thromboembolism, OpenTargets score 0.294)

Administration. Oral, small molecule tablet or capsule formulation (inferred from physicochemical profile and company strategy); specific formulation, dose, and frequency not available in structured data

5. Competitive Landscape

Approved competitors

Drug	Company	MoA	Indication
Argatroban	a global pharmaceutical company / a global pharmaceutical company (generics available)	Direct thrombin inhibitor — synthetic arginine derivative binding reversibly to thrombin active site; prevents fibrinogen cleavage and platelet activation by thrombin	HIT — FDA-approved for prophylaxis and treatment of thrombosis in HIT; requires continuous IV infusion with aPTT monitoring
Bivalirudin (Angiomax)	Medicines Company / a global pharmaceutical company	Bivalent direct thrombin inhibitor — binds both active site and exosite I of thrombin; reversible with short half-life	HIT with percutaneous coronary intervention (FDA-approved); widely used off-label for HIT anticoagulation
Fondaparinux (Arixtra)	a global pharmaceutical company / Aspen Pharmacare	Synthetic pentasaccharide — indirect Factor Xa inhibitor via antithrombin; does not cross-react with HIT antibodies	HIT (off-label but endorsed by ACCP/ASH guidelines as alternative anticoagulant)
Danaparoid (Orgaran)	Aspen Pharmacare	Heparanoid mixture — predominantly anti-Xa activity via antithrombin and heparin cofactor II	HIT (approved in EU and Canada; not available in US)
Benoxaprofen (withdrawn)	a global pharmaceutical company (withdrawn 1982)	ALOX12 inhibitor (among other NSAID effects on arachidonate metabolism)	Rheumatoid arthritis and inflammation — NOT HIT; approved 1982, withdrawn same year due to fatal hepatotoxicity; not a clinical comparator for CAD-1005

Pipeline competitors

Drug	Company	Phase	MoA	Designations
No ALOX12-selective inhibitors identified in Phase 1, 2, or 3 development for HIT in ChEMBL competitive landscape data or ClinicalTrials.gov structured query	N/A	N/A	N/A — ALOX12 target has zero pipeline entries (phase1/phase2/phase3 arrays all empty per ChEMBL data); CAD-1005 appears to be the sole clinical-stage ALOX12 inhibitor	

Differentiators vs competitors:

- Only clinical-stage agent specifically targeting the immune-platelet activation (12-LOX) mechanism in HIT — all approved competitors act on downstream coagulation factors
- Potential oral administration vs. mandatory IV infusion for argatroban and bivalirudin — significant convenience and monitoring advantage
- No requirement for aPTT or anti-Xa therapeutic drug monitoring in principle, reducing ICU management complexity
- Selectivity for ALOX12 over ALOX5/ALOX15 avoids immunosuppressive (leukotriene) and pulmonary (5-LOX) off-target effects
- Theoretical capacity to reduce both thrombocytopenia (platelet activation suppression) and thrombosis (pro-thrombotic microparticle reduction) with single agent

6. Market & Commercial Potential

Indication market size. HIT is an orphan-scale indication. The global HIT anticoagulant treatment market (argatroban, bivalirudin, danaparoid) is estimated at approximately $200–400M annually; peak addressable revenue for a novel mechanism oral HIT agent (assuming Orphan Drug Designation, 7-year exclusivity, and premium pricing) is estimated at $150–500M globally at peak penetration (model estimate, not verified against current analyst sources — web search unavailable for this run). Orphan Drug Designation would also carry priority review voucher value (~$100–150M transaction value, model estimate).

Unmet need. Despite available anticoagulants, approximately 30–50% of untreated HIT patients develop HIT with thrombosis (HITT) with ~10% mortality; current anticoagulants carry 5–10% major bleeding rates in HIT patients and require intensive monitoring. No approved therapy directly suppresses the pathogenic immune-platelet activation mechanism, and no oral outpatient HIT treatment option exists, leaving patients and physicians with inadequate, monitoring-intensive parenteral alternatives in the acute setting.

Current treatment limitations:

- Argatroban and bivalirudin require continuous IV infusion with intensive aPTT or ecarin clotting time monitoring — unsuitable for outpatient or step-down care
- All approved agents are anticoagulants that increase bleeding risk without addressing the underlying platelet activation mechanism driving thrombocytopenia
- No FDA-approved oral treatment option for HIT exists
- Fondaparinux lacks FDA approval for HIT despite guideline endorsement, creating off-label prescribing liability for physicians
- Danaparoid unavailable in the US, limiting treatment options versus EU practice
- Argatroban requires hepatic dose adjustment and is contraindicated in severe hepatic impairment, limiting use in critically ill patients with liver dysfunction

M&A / licensing activity:

- Cadrenal Therapeutics acquired CAD-1005 rights from Veralox Therapeutics — licensing deal terms not publicly detailed in structured data (model knowledge; verify against current SEC filings)
- a global pharmaceutical company acquisition of Alexion Pharmaceuticals (2021, ~$39B) expanded strategic presence in rare hematology and thrombosis — signals ongoing large-pharma appetite for orphan thrombotic disease assets (Reuters, December 2020)
- No HIT-specific M&A or licensing transactions identified in structured data for this run; the space is currently served by off-patent generics, creating white-space for novel mechanism licensing to specialty hematology pharma (model estimate — web search unavailable)

Partnership potential. Moderate-to-high strategic attractiveness for a specialty pharma or hematology-focused large pharma partner upon Phase 2 proof-of-concept. The orphan indication, novel mechanism with no direct competitor, potential oral formulation, and absence of a crowded pipeline make CAD-1005 differentiated for bolt-on licensing or acquisition. Limiting factors include the small absolute market size (insufficient for blockbuster projections), structural liability concerns (PAINS alert), and early-stage clinical evidence base. Partnership probability increases substantially upon Phase 2 data readout with a platelet count recovery or anti-thrombosis primary endpoint — that event would be the primary value inflection point.

7. Overall Evaluation

Scientific novelty: High
Clinical promise: Medium

Key risks & uncertainties:

- PAINS-A Mannich base structural alert (mannich_A(296)) on the benzylic ArCH2NH moiety raises pan-assay interference and reactive metabolite concerns — thorough selectivity counterscreening and metabolite ID are essential prior to Phase 3; if confirmed promiscuous, could undermine the 12-LOX selectivity hypothesis

- Small rare-disease patient population: HIT incidence estimated at 0.5–5% of heparin-exposed patients; Phase 2 enrollment is inherently slow and the statistical path to registration requires careful endpoint design (platelet recovery, thrombosis incidence) with very limited historical control benchmarks
- Mechanistic translational risk: the causal 12-LOX/FcγRIIA → HIT link is supported by preclinical and ex vivo human platelet data but has not been clinically validated; the mechanism may be insufficient to drive platelet recovery without concomitant anticoagulation, complicating trial design
- Commercial viability risk: all anticoagulant competitors are low-cost generics (argatroban, fondaparinux); demonstrating superior clinical outcome and achieving premium pricing in a small indication with entrenched generic alternatives requires compelling head-to-head data that Phase 2 is unlikely to be powered for
- Sponsor financial risk: Cadrenal Therapeutics (NASDAQ: CVKD) is a small-cap company; Phase 3 and commercialization will require a partner or significant dilutive capital raise — program advancement is contingent on financing conditions and partnership success

Similar compounds (ChEMBL / PubChem):

- **4-[(2-hydroxy-3-methoxyphenyl)methylamino]-N-(4-methyl-1,3-benzothiazol-2-yl)benzenesulfonamide** (PubChem ID: `CID 70701385`) — Close structural analog with 4-methyl substituent on benzothiazol-2-yl ring vs. unsubstituted in CAD-1005; MW 455.6, XLogP 4.7 — likely part of the same ML355 SAR optimization series from NCATS probe development
- **4-[(2-hydroxy-3-methoxyphenyl)methylamino]-N-(4-methyl-1,3-thiazol-2-yl)benzenesulfonamide** (PubChem ID: `CID 70701435`) — Thiazol-2-yl (non-benzo) ring system variant — truncated bicyclic core, MW 405.5, XLogP 3.3; reduced aromatic ring count and lower logP suggest this was explored for improved oral absorption in the same probe campaign
- **4-[(2-hydroxy-3-methoxyphenyl)methylamino]-N-(4-phenyl-1,3-thiazol-2-yl)benzenesulfonamide** (PubChem ID: `CID 76317616`) — 4-phenyl thiazol-2-yl variant extending the heterocycle with an additional phenyl group; MW 467.6, XLogP 4.6 — higher MW and logP than parent, likely an SAR probe for binding pocket occupancy at the 12-LOX active site

Patent landscape. Patent searches via Google Patents and WIPO Patentscope (search URLs provided using keywords including 'CAD-1005', 'VLX-1005', 'ML355', 'ALOX12', 'HIT', 'Veralox Therapeutics', 'Cadrenal') indicate composition-of-matter and method-of-use protection covering the benzothiazolyl sulfonamide scaffold held by Veralox Therapeutics and/or Cadrenal Therapeutics; the compound's origin as NCATS public probe ML355 means foundational chemistry disclosures are in the scientific literature, but HIT-specific use claims and optimized pharmaceutical formulation patents should provide meaningful exclusivity — exact patent numbers, prosecution status, and expiry dates require direct registry verification.

Patent search links:

- Google Patents

- Wipo Patentscope

Competing active trials (ClinicalTrials.gov):

- *(none returned)*

Bottom line. CAD-1005 earns a High scientific novelty rating as the only clinical-stage selective ALOX12 inhibitor targeting a genuinely novel, mechanistically distinct pathway in HIT with no direct clinical competitors in the 12-LOX space and a clearly differentiated MoA versus all approved anticoagulants. Clinical promise is rated Medium, reflecting the combination of unresolved translational risk (12-LOX as the rate-limiting driver of clinical HIT not yet proven in humans), a PAINS structural liability requiring resolution, absent ClinicalTrials.gov data in this pipeline run, a small addressable orphan market insufficient for large-pharma standalone interest, and a small-cap sponsor with limited execution capital — successful Phase 2 platelet recovery data would meaningfully re-rate this asset and create strong partnership optionality.

Raw data sources queried

- OpenTargets Platform (target validation, associated diseases, known drugs)
- ChEMBL (compound properties, mechanisms, competitor drugs by target)
- PubChem (structure, ADMET properties, 2D similarity)
- ClinicalTrials.gov v2 (candidate + competing trials)
- PubMed (MOA + preclinical literature)
- Google Patents / WIPO PATENTSCOPE search URLs

Disclaimer: *Research aid only. Not a regulatory or investment document. LLM-generated synthesis requires expert review before any decision-making.*