

ABSTRACT

Omecamtiv Mecarbil

Omecamtiv mecarbil (CK-1827452, AMG 423) is a first-in-class selective small-molecule activator of cardiac myosin, the beta-myosin heavy chain (MYH7) motor protein of the ventricular sarcomere. Discovered at Cytokinetics, Inc. through high-throughput screening of a reconstituted calcium-responsive sarcomere assay and advanced through extensive structure-activity optimization from a poorly soluble nitro-aromatic hit compound, omecamtiv mecarbil binds an allosteric pocket on the cardiac myosin catalytic domain (SI subfragment) that stabilizes the lever arm in a primed, pre-powerstroke conformation. The compound accelerates the rate-limiting phosphate release step of the cross-bridge cycle, increasing the number of myosin heads engaged with the actin filament during systole and prolonging the duration of force generation, without increasing intracellular calcium concentration or myocardial oxygen consumption. X-ray crystallographic studies have resolved the binding site at 2.45 Angstrom resolution, revealing interactions with the converter domain, relay helix, and N-terminal subdomain that induce a 15-degree rotation and approximately 4 Angstrom translation of the converter. Selectivity for cardiac over skeletal and smooth muscle myosin is structurally rationalized by divergent converter domain residues across isoforms. The clinical development program, spanning nine Phase 1 studies, four Phase 2 trials, and two Phase 3 trials over more than a decade, has established the pharmacodynamic signature of omecamtiv mecarbil:

concentration-dependent prolongation of systolic ejection time, increased stroke volume and ejection fraction, decreased ventricular volumes, and reduced NT-proBNP, achieved without

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the tachycardia, hypotension, or proarrhythmic signals characteristic of catecholamine-based inotropes. The pivotal GALACTIC-HF trial (n = 8,256; NCT02929329) demonstrated a statistically significant reduction in the primary composite endpoint of cardiovascular death or first heart failure event (hazard ratio 0.92; 95% CI 0.86 to 0.99; p = 0.03), with the treatment benefit concentrated among patients with the lowest baseline ejection fractions (LVEF 22% or below: HR 0.83; 95% CI 0.73 to 0.95) and highest NT-proBNP levels. Cardiovascular death alone was not significantly reduced (HR 1.01). The METEORIC-HF trial (n = 276; NCT03759392) found no significant improvement in peak exercise capacity over 20 weeks, indicating that the cardiovascular outcomes benefit may operate through reduction of heart failure decompensation events rather than augmented peak aerobic performance. Pharmacokinetics are characterized by high oral bioavailability (approximately 93%), a terminal half-life of approximately 18 to 21 hours supporting twice-daily dosing, metabolism primarily through a decarbamylation pathway with modest CYP3A4 and CYP2D6 contributions, and balanced renal and fecal elimination. Omecamtiv mecarbil does not prolong the QTc interval at therapeutic concentrations. The compound received a Complete Response Letter from the United States Food and Drug Administration in February 2023; a confirmatory Phase 3 trial (COMET-HF) in patients with severely reduced ejection fraction is ongoing with expected completion in 2028. This monograph reviews the chemistry, structural pharmacology, comprehensive pharmacokinetic characterization, the complete clinical evidence base including positive and negative trials with subgroup analyses, the sourcing and handling considerations for research applications, and a comparative assessment of five heart failure agents against omecamtiv mecarbil on five competency

standards. The compound is investigational and is not approved by any regulatory authority.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Omecamtiv mecarbil.

Development codes: CK-1827452 (Cytokinetics), AMG 423 (Amgen), EX-A714, CK-452. The CK-1827452 designation is the canonical identifier in the early pharmacology and medicinal chemistry literature [1].

Chemical Abstracts Service registry number: 873697-71-3 (free base).

International Union of Pure and Applied Chemistry name: Methyl 4-[[2-fluoro-3-[(6-methylpyridin-3-yl)carbamoylamino]phenyl]methyl]piperazine-1-carboxylate [1, 2].

Database identifiers: PubChem CID 11689883; ChEMBL CHEMBL1800955; DrugBank DB11816; UNII 2M19539ERK.

1.2 Structural class and chemistry

Omecamtiv mecarbil is a synthetic small-molecule diaryl urea containing a fluorinated phenyl ring bridged to a methylpiperazine carbamate through a benzylamine linker. The structural architecture comprises three pharmacophoric elements: a 6-methylpyridin-3-amine head group linked via a urea bond to a 2-fluoro-3-substituted aniline core, with a methyl piperazine-1-carboxylate tail [1].

Molecular formula: C₂₀H₂₄FN₅O₃ (free base).

Molecular weight: 401.44 g/mol (free base) [2].

Exact mass: 401.1863 g/mol (monoisotopic) [2].

Canonical	SMILES:
<chem>CC1=NC=C(C=C1)NC(=O)NC2=CC=CC(=C2F)CN3CCN(CC3)C(=O)OC</chem> [2].	

InChIKey: RFUBTTPMWSKEIW-UHFFFAOYSA-N [2].

Computed physical properties: XLogP 1.4; topological polar surface area 86.8 square Angstroms; hydrogen bond donors 2; hydrogen bond acceptors 6; pKa 6.1 [1, 2].

Salt forms: The dihydrochloride monohydrate salt ($C_{20}H_{24}FN_5O_3 \cdot 2HCl \cdot H_2O$) is used in clinical formulations [15]. The free base is the standard research-grade form.

Stereochemistry: Omecamtiv mecarbil is achiral and contains no stereocenters. The compound does not require enantiomeric purity characterization.

Physical properties: White to off-white crystalline powder. Freely soluble in dimethyl sulfoxide; soluble in methanol and ethanol; sparingly soluble in water as the free base. The dihydrochloride salt has improved aqueous solubility suitable for intravenous and oral formulations.

1.3 Synthesis

The discovery synthesis of omecamtiv mecarbil was disclosed by Morgan et al. (2010) from Cytokinetics [1]. The medicinal chemistry campaign began from a poorly soluble, nitro-aromatic hit compound (compound 1) identified through high-throughput screening of a fully soluble, calcium-responsive, reconstituted sarcomere assay measuring increases in cardiac myosin ATPase activity. The optimization addressed multiple liabilities simultaneously: the nitro group (genotoxicity concern), hydrolytic instability of the diaryl amide, poor aqueous solubility, low free fraction, modest intrinsic potency, off-target vasodilatory activity through KATP channel inhibition, CYP 1A2 inhibition, and high intrinsic clearance [1]. Through systematic variation of three pharmacophoric regions and evaluation of approximately 24 intermediate compounds across four optimization tables, the campaign converged on compound 24 (omecamtiv mecarbil). The final compound achieved an AC40 of 0.58 micromolar in the reconstituted sarcomere assay (where AC40 is the concentration producing a 40 percent increase in cardiac sarcomere ATPase activity at submaximal calcium), representing approximately a 2.5-fold potency improvement over the original hit (AC40 approximately 1.4 micromolar), combined with substantially improved selectivity, metabolic stability (clearances of 22 mL/min/kg in rats and 7.2 mL/min/kg in dogs), and oral bioavailability (100 percent in rats, 80 percent in dogs) [1]. The synthetic route proceeds through standard urea formation between the substituted aniline and the aminopyridine, followed by re-

ductive amination or alkylation to install the piperazine carbamate moiety. Industrial process chemistry details have been disclosed in patent US 9,988,354 (salt preparation).

2. Abstract

Omecamtiv mecarbil (CK-1827452) is a first-in-class selective small-molecule activator of cardiac myosin that binds an allosteric pocket on the catalytic S1 domain of the beta-myosin heavy chain and increases ventricular contractility through a mechanism fundamentally distinct from all prior inotropic agents [1, 2]. Rather than increasing intracellular calcium or cyclic AMP, omecamtiv mecarbil stabilizes the myosin lever arm in the primed, pre-powerstroke state, accelerating the rate-limiting phosphate release step and increasing the number of force-generating cross-bridges available at the onset of systole [11]. X-ray crystallographic studies at 2.45 Angstrom resolution have defined the binding site and the conformational changes it induces in the converter domain and relay helix [11]. In vitro, the compound increases the actin-activated ATPase rate approximately twofold while paradoxically suppressing the individual myosin working stroke, achieving net force enhancement through cooperative thin-filament activation [12, 16].

The clinical development program established the pharmacodynamic signature: concentration-dependent increases in systolic ejection time (up to 85 ms at the maximum tolerated intravenous dose), stroke volume, and ejection fraction, with concomitant decreases in ventricular volumes, heart rate, and NT-proBNP [3, 4, 10]. The pivotal GALACTIC-HF trial in 8,256 patients with chronic HFrEF demonstrated a significant 8 percent relative risk reduction in the primary composite of cardiovascular death or first heart failure event (HR 0.92; 95% CI 0.86 to 0.99; $p = 0.03$), with the benefit concentrated in patients with the lowest ejection fractions (LVEF 22% or below: HR 0.83) [18, 19]. The METEORIC-HF trial found no improvement in peak exercise capacity [25]. The compound received a Complete Response Letter from the FDA in February 2023; a confirmatory Phase 3 trial (COMET-HF) in patients with severely reduced ejection fraction is ongoing.

Pharmacokinetics are favorable for chronic oral dosing: high bioavailability (approximately 93%), moderate protein binding (approximately 82%), a terminal half-life of 18 to 21 hours, metabolism primarily by a decarbamylation pathway, and no QTc prolongation at therapeutic concentrations [7, 8, 21, 23]. This monograph documents the chemistry, structural pharmacology, the comprehensive pharmacokinetic record, the complete clinical evidence base across all studied endpoints in-

cluding both positive and negative trial outcomes, the sourcing and handling considerations for laboratory work, and a comparative assessment of five heart failure therapeutic agents on five competency standards.

3. Discovery and Development History

3.1 Origin

Omecamtiv mecarbil was discovered at Cytokinetics, Inc. (South San Francisco, California) as part of a systematic effort to identify the first selective small-molecule activator of cardiac myosin [1]. The discovery program used computer-aided design and high-throughput screening of a reconstituted sarcomere preparation to find compounds with specific affinity for beta-cardiac myosin [1, 2]. Morgan et al. (2010) published the discovery synthesis in ACS Medicinal Chemistry Letters, documenting the progression from the original HTS hit (compound 1, a poorly soluble nitro-aromatic with an AC40 of approximately 1.4 micromolar) through iterative optimization to omecamtiv mecarbil (compound 24, AC40 0.58 micromolar), a compound suitable for clinical development [1].

3.2 Preclinical characterization

Malik et al. (2011) published the definitive preclinical characterization in Science, establishing the pharmacological principle that selective cardiac myosin activation could improve systolic function in the intact heart [2]. In conscious dogs with heart failure, omecamtiv mecarbil (bolus and 24-hour infusion) increased systolic wall thickening, stroke volume, and cardiac output while reducing heart rate, peripheral vascular resistance, mean left atrial pressure, and left ventricular end-diastolic pressure [2, 15]. Critically, the compound increased the duration of ejection without changing the rates of contraction and without increasing myocardial oxygen consumption [2]. In a key mechanistic finding, Malik et al. reported that omecamtiv mecarbil inhibits ATP turnover in the absence of actin, suggesting stabilization of a pre-powerstroke state that becomes catalytically active upon actin engagement [2].

3.3 Clinical development

The clinical development program began with nine Phase 1 studies in over 200 healthy volunteers, followed by four Phase 2 studies in more than 1,300 heart failure patients [15]. The first-in-human study (Teerlink et al. 2011, Lancet) established dose-dependent augmentation of cardiac systolic function and identified a maxi-

mum tolerated intravenous dose of 0.5 mg/kg/h [3]. The Phase 2a crossover study (Cleland et al. 2011, Lancet) confirmed the concentration-response relationship in heart failure patients [4]. ATOMIC-AHF (Teerlink et al. 2016, JACC) tested intravenous omecamtiv mecarbil in acute heart failure and found no improvement in the primary dyspnea endpoint but significant hemodynamic effects and favorable tolerability [9]. COSMIC-HF (Teerlink et al. 2016, Lancet) established the oral pharmacokinetic-guided dosing regimen of 25 to 50 mg twice daily that would be used in the pivotal Phase 3 program [10].

3.4 Partnership history and regulatory trajectory

Cytokinetics partnered with Amgen in 2006 for the global development and commercialization of omecamtiv mecarbil. Amgen co-funded the Phase 3 GALACTIC-HF trial (NCT02929329), which enrolled 8,256 patients and reported positive primary results in November 2020 [18]. In November 2020, Amgen announced its intention to transition development and commercial rights for omecamtiv mecarbil back to Cytokinetics [15]. Servier subsequently provided funding and strategic support for the program.

Cytokinetics submitted a New Drug Application to the FDA based on GALACTIC-HF. In February 2023, the FDA issued a Complete Response Letter, determining that the GALACTIC-HF data alone were not sufficiently persuasive to establish substantial evidence of effectiveness for reducing the risk of heart failure events and cardiovascular death. Cytokinetics filed a Formal Dispute Resolution Request, which the FDA denied in 2024, reaffirming the need for confirmatory evidence. A Type C meeting between Cytokinetics and the FDA addressed the design features of a confirmatory Phase 3 trial. Cytokinetics initiated COMET-HF (Confirmation of Omecamtiv Mecarbil Efficacy Trial in Heart Failure), which targets approximately 1,800 patients with symptomatic heart failure and LVEF below 30 percent, enriching for the subgroup that demonstrated the greatest benefit in GALACTIC-HF [32]. COMET-HF is expected to complete enrollment in 2026 with results anticipated by 2028. A Marketing Authorization Application was also submitted to the European Medicines Agency, with Day 180 outstanding issues received in Q4 2023.

4. Mechanism of Action

Omecamtiv mecarbil is a multi-level cardiac myosin activator whose molecular mechanism has been characterized through X-ray crystallography, transient-state kinetics, single-molecule mechanics, and functional studies in isolated cardiomyocytes and intact hearts. The principal molecular activity is allosteric activation of the beta-myosin heavy chain (MYH7), the force-generating motor protein of the ventricular sarcomere.

4.1 Primary molecular target and allosteric binding site

The primary target is the catalytic motor domain (subfragment-1, S1) of cardiac myosin. Omecamtiv mecarbil binds an allosteric pocket distinct from the nucleotide-binding site and the actin-binding interface. Planelles-Herrero et al. (2017) solved the crystal structure of the cardiac myosin motor domain in complex with omecamtiv mecarbil in the pre-powerstroke state at 2.45 Angstrom resolution (PDB code 5N69), alongside an apo structure at 3.10 Angstrom resolution (PDB code 5N6A) [11]. The binding pocket, designated the "PPS allosteric site," is formed at the junction of the N-terminal subdomain (residues K146, R147, N160, Q163, Y164, T167, D168), the relay helix (H492), the transducer region (H666), and the converter domain (P710, N711, R712, I713, R721, Y722, F765, L770, E774) [11]. This pocket is separated by more than 18 Angstroms from a previously described binding site in the post-rigor state [11].

Winkelmann et al. (2015) independently solved the structure of the human cardiac myosin catalytic domain bound to omecamtiv mecarbil (PDB codes 4P7H and 4PA0), reporting that the compound occupies a narrow cleft between the N-terminal 25-kDa domain and the lower 50-kDa domain, with key interactions involving a buried bidentate salt bridge between E497 and R712 and contacts with residues C705, S118, A91, M92, and F121 [5]. Winkelmann et al. measured an apparent K_i of 100 to 150 nM for the human cardiac myosin catalytic domain and cardiac heavy meromyosin [5].

Binding of omecamtiv mecarbil induces a 15-degree rotation and approximately 4 Angstrom translation of the converter subdomain, along with a 6 Angstrom displacement of the relay helix, locking the lever arm in a fully primed, pre-power-

stroke orientation [11]. The binding is strictly nucleotide-state dependent: isothermal titration calorimetry revealed a K_d of 0.29 ± 0.04 micromolar with MgADP.VO₄ (the post-hydrolysis ADP.Pi analog), 1.80 ± 0.21 micromolar with ADP-BeFx, 2.80 ± 0.37 micromolar with AMPPNP, and 5.3 ± 1.8 micromolar with MgADP alone; no binding was detected in the nucleotide-depleted state [11].

4.2 Enzymatic mechanism: ATPase activation and phosphate release

Omecamtiv mecarbil accelerates the rate-limiting step of the cardiac myosin cross-bridge cycle: the transition from the weakly bound pre-powerstroke state to the strongly bound force-generating state, governed by phosphate release from the active site [2, 11, 12]. Rohde et al. (2017) quantified the kinetic effects using transient-state fluorescence spectroscopy on bovine cardiac myosin subfragment-1 [12]. In the absence of drug, the maximal rate of actin-activated phosphate release was 11.6 per second (K_m for actin = 15.5 micromolar). In the presence of omecamtiv mecarbil, the maximal rate approximately doubled to 22.1 per second (K_m for actin = 26.2 micromolar) [12]. Paradoxically, while omecamtiv mecarbil accelerated phosphate release, it simultaneously slowed the actin-activated powerstroke: the rate decreased from 15.3 per second (K_m = 35.5 micromolar) to 2.05 per second (K_m = 5.85 micromolar) [12]. This indicates that omecamtiv mecarbil decouples the temporal relationship between the powerstroke and phosphate release.

Woody et al. (2018) extended this analysis using single-molecule optical trapping, reporting that omecamtiv mecarbil "suppresses myosin's working stroke and prolongs actomyosin attachment 5-fold" [16]. The net force enhancement arises through "cooperative thin-filament activation by OM-inhibited myosin molecules" [16]; prolonged attachment of drug-bound myosin heads to actin enhances overall thin-filament activation at intermediate calcium concentrations, recruiting additional myosin heads into force-generating states. Woody et al. described this as "an unanticipated route to muscle activation" through selective suppression of myosin [16].

4.3 Selectivity for cardiac myosin

Omecamtiv mecarbil demonstrates selectivity for the cardiac sarcomere over both fast skeletal muscle myosin and smooth muscle myosin. The original HTS hit "demonstrated excellent selectivity for the cardiac sarcomere over the skeletal sar-

comere and smooth muscle myosin" [1], confirmed by comparing actin-stimulated ATPase activity across a panel of myosin isoforms (cardiac bovine, skeletal rabbit, smooth muscle bovine uterus and chicken gizzard) [1]. Winkelmann et al. confirmed that adult fast skeletal muscle myosin was essentially unaffected even at the highest omecamtiv mecarbil concentrations tested [5]. The selectivity is structurally rationalized by the involvement of converter domain residues in the allosteric binding pocket that diverge between cardiac and skeletal isoforms [5, 11]. Additionally, omecamtiv mecarbil showed no vasodilatory activity (aortic ring R50 greater than 25 micromolar), no CYP 1A2 inhibition (IC50 greater than 10 micromolar), and no effect on cardiomyocyte calcium transients [1].

4.4 Downstream physiological effects in isolated myocardium

In freshly isolated adult rat cardiomyocytes, omecamtiv mecarbil at 0.2 micromolar increased fractional shortening by 123 percent without affecting the intracellular calcium transient [1]. Raduly et al. (2023) characterized the concentration-dependent effects in more detail, observing dose-dependent decreases in resting sarcomere length (from 1.96 $\pm$ 0.01 micromolar at baseline to 1.50 $\pm$ 0.05 micromolar at 1 micromolar omecamtiv mecarbil) and marked prolongation of contraction duration (from 0.95 $\pm$ 0.05 seconds at baseline to 5.89 $\pm$ 0.57 seconds at 1 micromolar), while calcium transient amplitudes remained unchanged [28]. These findings implicate a narrow therapeutic window, with a risk of impaired relaxation at supratherapeutic concentrations [28].

Mamidi et al. (2017) evaluated omecamtiv mecarbil at 0.5 and 1.0 micromolar in chemically skinned myocardial preparations from human donor and failing hearts [13]. Force enhancements were pronounced at submaximal calcium activations but declined as calcium was increased toward maximum. The 1.0 micromolar concentration induced slowing of the cross-bridge detachment rate (k_{rel}) in failing myocardium, whereas the 0.5 micromolar concentration enhanced force without this kinetic penalty [13], suggesting that optimal dosing is critical for systolic benefit without diastolic impairment.

Varzideh et al. (2023) confirmed this concern in living myocardial slices from patients with end-stage heart failure, reporting that omecamtiv mecarbil significantly increases contractile force and time-to-peak but also slows relaxation, with the re-

laxation impairment further aggravated at faster heart rates [29]. These findings suggest limited utility in heart failure conditions with prevalent diastolic dysfunction [29].

4.5 Composite pharmacology at therapeutic concentrations

At the organ level in conscious dogs with heart failure, omecamtiv mecarbil produced concentration-dependent increases in systolic wall thickening, stroke volume, and cardiac output while reducing heart rate, vascular resistance, and left atrial and left ventricular end-diastolic pressures [2, 15]. In the first-in-human study, intravenous omecamtiv mecarbil at the maximum tolerated dose (0.5 mg/kg/h) increased systolic ejection time by a mean of 85 +/- 5 milliseconds, stroke volume by 15 +/- 2 mL, fractional shortening by 8 +/- 1 percent, and ejection fraction by 7 +/- 1 percent (all $p < 0.0001$) [3]. Population pharmacokinetic-pharmacodynamic modeling estimated a maximum possible systolic ejection time increase of 137 milliseconds, with left ventricular outflow tract stroke volume increasing linearly by 1.6 mL per 100 ng/mL of omecamtiv mecarbil [7]. Systolic ejection time was the most sensitive indicator of drug effect (r -squared = 0.99 by dose) [3].

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Omecamtiv mecarbil is rapidly and extensively absorbed after oral administration. The absolute oral bioavailability of the solution formulation is 93.5 percent [21]. For the immediate-release (IR) formulation at a 25 mg dose, the median time to peak plasma concentration (T_{max}) is 0.5 hours in the fasted state, with a mean C_{max} of 262 +/- 81 ng/mL and AUC-infinity of 2,490 +/- 432 h*ng/mL [8]. Modified-release (MR) tablet formulations reduced C_{max} by 70 percent or more while maintaining comparable total exposure, with T_{max} values of 2 to 10 hours depending on formulation design [8]. Food decreased the IR C_{max} by 45 percent (fed/fasted ratio 0.55) and approximately doubled T_{max} from 0.5 to 2.0 hours without meaningfully affecting total exposure (AUC-infinity ratio 0.99; 90% CI 0.93 to 1.05) [8]. Food had a marginal, nonclinically meaningful effect on the MR formulations [8].

5.2 Distribution

The volume of distribution is moderate: 3.5 L/kg in rats and 3.6 L/kg in dogs [1]. Plasma protein binding in humans is approximately 82 percent [1, 15]. Population pharmacokinetic analysis described the disposition as a linear two-compartment model with first-order oral absorption [7]. The effective unbound plasma concentration at therapeutic doses is below 200 nanomolar, comparable to the K_d for myosin heads in the MgADP.VO₄ state (0.29 micromolar), indicating pharmacologically relevant target occupancy [11].

5.3 Metabolism

Omecamtiv mecarbil undergoes oxidative metabolism primarily through a decarbamylation pathway. In a radiolabeled (¹⁴C) ADME study in 14 healthy male subjects, unchanged omecamtiv mecarbil accounted for 83.8 percent of total plasma radioactivity, with two principal metabolites: M3 (the des-carbamoyl metabolite, 6.0 percent of plasma radioactivity) and M4 (the lactam of M3, 3.3 percent) [21]. The

formation of M3 is primarily catalyzed by the CYP4 family of enzymes, with modest contributions from CYP3A4 and CYP2D6 [20, 21]. In excreta, M3 accounted for 26.5 percent and M4 for 11.6 percent of the administered dose [21].

5.4 Elimination

The mean terminal elimination half-life is approximately 18 to 21 hours across formulations and study populations, consistent between fasted and fed states [7, 8]. Total recovery of radiolabeled drug was 86.5 percent over 336 hours after oral dosing, with 48.6 percent recovered in urine and 38.0 percent in feces [21]. Unchanged parent compound accounted for only 7.7 percent in urine and 4.1 percent in feces, indicating that elimination occurs predominantly as metabolites [21]. In preclinical species, clearance was 22 mL/min/kg in rats and 7.2 mL/min/kg in dogs [1].

5.5 Drug-drug interactions

Two dedicated interaction studies evaluated CYP-mediated interactions [20]. Coadministration with ketoconazole (a potent CYP3A4 inhibitor) in CYP2D6 extensive metabolizers produced a 51 percent increase in omecamtiv mecarbil AUC-infinity while C_{max} remained similar (3 percent higher) [20]. In CYP2D6 poor metabolizers, ketoconazole increased AUC-infinity by only 31 percent [20]. Coadministration with diltiazem produced no changes in omecamtiv mecarbil pharmacokinetics in extensive metabolizers [20]. As a perpetrator, omecamtiv mecarbil caused an 18 percent decrease in midazolam AUC-infinity, indicating minimal CYP3A4 induction potential [20]. Coadministration with omeprazole (a proton pump inhibitor and CYP2C19 inhibitor) did not meaningfully alter omecamtiv mecarbil pharmacokinetics [27]. The investigators concluded that CYP3A4 and CYP2D6 inhibitors are unlikely to have a clinically significant effect on the pharmacokinetics of omecamtiv mecarbil [20].

5.6 Special populations

In subjects with mild hepatic impairment (Child-Pugh A), omecamtiv mecarbil AUC-infinity was 103.2 percent of normal (90% CI 58.0 to 183.6%), and in moderate impairment (Child-Pugh B), AUC-infinity was 94.8 percent of normal (90% CI 54.7 to 164.1%) [22]. The same dosing strategy can be used in subjects with mild or moder-

ate hepatic impairment [22]. Severe hepatic impairment (Child-Pugh C) has not been studied. Population pharmacokinetic analysis found that variability in pharmacokinetic parameters was not explained by standard demographic covariates [7].

5.7 QTc assessment

A thorough QT study (NCT04175808) evaluated a single 50 mg oral dose of omecamtiv mecarbil in a three-period, three-treatment, six-sequence crossover study in 60 healthy subjects with moxifloxacin as positive control [23]. The mean placebo-corrected change from baseline QTcF (ddQTcF) ranged from -6.7 ms at 1 hour postdose to -0.8 ms at 4 hours postdose, with a maximum upper bound of the one-sided 95 percent confidence interval of 0.7 ms [23]. An effect on ddQTcF exceeding 10 ms can be excluded up to plasma concentrations of approximately 800 ng/mL, well above the therapeutic range [23]. In vitro proarrhythmic assays have confirmed low proarrhythmic risk [23].

5.8 Routes of administration

Two principal routes have been studied: intravenous infusion (Phase 1 and Phase 2 acute studies, doses of 0.005 to 1.0 mg/kg/h over 2 to 72 hours) and oral modified-release tablets (Phase 2b and Phase 3 chronic studies, doses of 25, 37.5, or 50 mg twice daily guided by pharmacokinetic monitoring) [3, 4, 10, 18].

6. Clinical Evidence Base

The clinical evidence base for omecamtiv mecarbil represents one of the most extensive development programs for a novel inotropic mechanism, spanning more than a decade from first-in-human dosing through pivotal Phase 3 cardiovascular outcomes trials. Investigators evaluating the compound for research applications should note that omecamtiv mecarbil is investigational and is not approved by any regulatory authority; all clinical data presented are from published peer-reviewed studies conducted under institutional review board or ethics committee oversight.

6.1 Phase 1: first-in-human intravenous dose escalation

Teerlink et al. (2011) conducted a double-blind, placebo-controlled, dose-escalation study in 34 healthy men who received 6-hour intravenous infusions of omecamtiv mecarbil or placebo once weekly for four weeks, with three ascending doses ranging from 0.005 to 1.0 mg/kg/h in a crossover design [3]. The maximum tolerated dose was 0.5 mg/kg/h. At this dose, systolic ejection time increased by a mean of 85 (SD 5) ms, stroke volume rose by 15 (2) mL, fractional shortening improved by 8% (1), and ejection fraction increased by 7% (1); all $p < 0.0001$ [3]. The dose-limiting toxicity was myocardial ischemia due to excessive prolongation of systolic ejection time at the highest tested dose [3].

6.2 Phase 2a: dose-ranging crossover trial

Cleland et al. (2011) evaluated intravenous omecamtiv mecarbil in 45 patients with stable chronic heart failure and left ventricular systolic dysfunction in a double-blind, placebo-controlled, crossover design with 151 total infusions over durations of 2, 24, or 72 hours [4]. Concentration-dependent improvements included systolic ejection time increases of up to 80 ms, stroke volume gains of up to 9.7 mL, and heart rate reductions of up to 2.7 beats per minute ($p < 0.0001$) [4]. Higher concentrations reduced end-systolic volume by 15 mL ($p = 0.0026$) and end-diastolic volume by 16 mL ($p = 0.0096$) [4]. Cardiac ischemia occurred in two patients at elevated plasma concentrations (approximately 1750 and 1350 ng/mL), establishing an upper boundary for the therapeutic concentration range [4].

6.3 Phase 2: ATOMIC-AHF

ATOMIC-AHF (Acute Treatment with Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure) enrolled 606 patients with acute heart failure and LVEF 40 percent or below, randomized to double-blind, 48-hour intravenous infusion of placebo or omecamtiv mecarbil in three sequential, escalating-dose cohorts [9]. The primary endpoint of dyspnea relief at 48 hours was not met (placebo 41%, omecamtiv mecarbil pooled 47%, $p = 0.33$) [9]. However, omecamtiv mecarbil produced concentration-related increases in systolic ejection time ($p < 0.0001$) and decreases in end-systolic dimension ($p < 0.05$) [9]. In supplemental analyses, the highest-dose cohort showed greater dyspnea relief at 48 hours compared with placebo (51% vs 37%, $p = 0.034$) [9]. Plasma troponin concentrations were modestly higher in the omecamtiv mecarbil group (median difference 0.004 ng/mL at 48 hours) without a clear concentration-response relationship ($p = 0.95$) [9]. The adverse event profile was similar to placebo, without increases in ventricular or supraventricular tachyarrhythmias [9].

6.4 Phase 2b: COSMIC-HF

COSMIC-HF (Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure) was the pivotal Phase 2 study bridging intravenous to oral dosing [10]. This was a phase 2, pharmacokinetic, randomized, placebo-controlled trial conducted at 87 sites in 13 countries, enrolling 448 patients with chronic heart failure and LVEF 40 percent or below [10]. Patients were randomized to fixed-dose omecamtiv mecarbil 25 mg twice daily, PK-titrated omecamtiv mecarbil (25 mg twice daily titrated to 50 mg twice daily), or placebo for 20 weeks [10]. Mean maximum concentration at 12 weeks was 200 (SD 71) ng/mL in the fixed-dose group and 318 (129) ng/mL in the PK-titration group [10].

The PK-titration group demonstrated significant improvements at 20 weeks versus placebo: systolic ejection time increased by 25 ms (95% CI 18 to 32, $p < 0.0001$), stroke volume improved by 3.6 mL (0.5 to 6.7, $p = 0.0217$), left ventricular end-systolic diameter decreased by 1.8 mm (-2.9 to -0.6, $p = 0.0027$), and left ventricular end-diastolic diameter decreased by 1.3 mm (-2.3 to 0.3, $p = 0.0128$) [10]. Heart rate decreased by 3.0 beats per minute (-5.1 to -0.8, $p = 0.0070$), and NT-proBNP decreased by 970 pg/mL (-1672 to -268, $p = 0.0069$) [10]. Troponin increased modestly: median change from baseline at week 20 was 0.001 ng/mL in the fixed-dose group

and 0.006 ng/mL in the PK-titration group; none were judged due to myocardial ischemia or infarction [10, 15]. The frequency of adverse clinical events did not differ between groups [10].

6.5 Phase 3: GALACTIC-HF

GALACTIC-HF (Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure) was the pivotal Phase 3 cardiovascular outcomes trial: an international, multicenter, randomized, double-blind, placebo-controlled, event-driven study in 8,256 patients with chronic HFrEF (LVEF 35% or below, NYHA class II to IV) at more than 800 sites across 35 countries [17, 18]. Omecamtiv mecarbil was administered using a pharmacokinetic-guided dose titration strategy using doses of 25, 37.5, or 50 mg twice daily on top of standard-of-care therapy [17].

The primary composite endpoint of time to cardiovascular death or first heart failure event was met, with a hazard ratio of 0.92 (95% CI 0.86 to 0.99; $p = 0.03$), representing an 8 percent relative risk reduction [18]. A primary endpoint event occurred in 37.0 percent of the omecamtiv mecarbil group versus 39.1 percent of the placebo group [18]. The benefit was driven primarily by reduction in heart failure events. Cardiovascular death alone was not significantly reduced (HR 1.01; 95% CI 0.92 to 1.11) [18].

Prespecified subgroup analyses revealed important treatment effect modification. Ejection fraction was the strongest modifier: in the lowest EF quartile (LVEF 22% or below, $n = 2,246$), the hazard ratio was 0.83 (95% CI 0.73 to 0.95), representing an absolute risk reduction of 7.4 events per 100 patient-years and a number needed to treat over 3 years of 11.8 [19]. In the highest EF quartile (LVEF 33% or above), the hazard ratio was 0.99 (95% CI 0.84 to 1.16), with a significant interaction ($p = 0.013$ by quartile, $p = 0.004$ as continuous variable) [19]. Among patients without atrial fibrillation or flutter, those above the median NT-proBNP (median 1,675 pg/mL) showed a hazard ratio of 0.81 (95% CI 0.73 to 0.90), while those at or below the median had a hazard ratio of 0.94 (95% CI 0.80 to 1.09) [24]. Patients with systolic blood pressure 100 mmHg or below ($n = 1,473$) showed a hazard ratio of 0.81 (95% CI 0.70 to 0.94; $p = 0.005$) versus 0.95 (95% CI 0.88 to 1.03) for those above 100 mmHg, with NT-proBNP reductions of 18 percent versus 9 percent respectively [26].

The safety profile was favorable: rates of myocardial ischemia, ventricular arrhythmias, and death were similar between groups across nearly 7,500 patient-years of follow-up [18]. There were no detrimental effects on blood pressure, heart rate, creatinine, or potassium [18].

6.6 Phase 3: METEORIC-HF (negative trial)

METEORIC-HF (NCT03759392) was a randomized, placebo-controlled, double-blind study in 276 patients with HFrEF (LVEF 35% or below, NYHA class II to III) evaluating the effect of omecamtiv mecarbil on exercise capacity over 20 weeks [25]. The primary endpoint was the change in peak oxygen consumption (peak VO₂). The trial was negative: mean change was -0.24 mL/kg/min with omecamtiv mecarbil versus 0.21 mL/kg/min with placebo (least-squares mean difference -0.45 mL/kg/min; 95% CI -1.02 to 0.13; p = 0.13) [25]. Secondary endpoints (ventilatory efficiency, daily activity, peak workload) were also non-significant [25]. The disconnect between the cardiovascular outcomes benefit in GALACTIC-HF and the absence of exercise capacity improvement in METEORIC-HF suggests that the clinical benefit may operate through reduction of heart failure decompensation events and ventricular remodeling rather than augmented peak aerobic performance [25].

6.7 Exercise safety in ischemic cardiomyopathy

Greenberg et al. (2015) evaluated the safety and tolerability of intravenous omecamtiv mecarbil during exercise in patients with ischemic cardiomyopathy and angina in a double-blind, placebo-controlled trial [6]. At doses producing plasma concentrations previously shown to increase systolic function, omecamtiv mecarbil was well tolerated during exercise, with the proportion of patients stopping exercise testing because of angina at an earlier stage than baseline observed in 1 patient receiving placebo and none receiving omecamtiv mecarbil [6].

7. Reported Research Dose Ranges

7.1 Intravenous doses (acute and research applications)

Phase 1 and Phase 2 intravenous dose ranges: 0.005 to 1.0 mg/kg/h over 2 to 72 hours [3, 4]. The maximum tolerated intravenous dose is 0.5 mg/kg/h over 6 hours in healthy volunteers [3]. In heart failure patients, concentrations above approximately 1,200 to 1,750 ng/mL are associated with cardiac ischemia from excessive systolic ejection time prolongation [4]. The therapeutic target plasma concentration range for cardiac hemodynamic effects is approximately 200 to 600 ng/mL [4, 10].

7.2 Oral doses (chronic dosing)

The PK-guided oral dosing strategy established in COSMIC-HF and used in GALACTIC-HF and METEORIC-HF employs doses of 25, 37.5, or 50 mg twice daily, titrated on the basis of plasma drug concentrations measured at week 2 and week 6 [10, 18]. Target trough plasma concentrations for dose titration are 200 to 400 ng/mL [10]. In GALACTIC-HF, the majority of patients were maintained on 25 or 50 mg twice daily after titration [18].

Investigators acquiring research-grade omecamtiv mecarbil should note that the PK-guided dosing strategy was integral to the clinical benefit observed in GALACTIC-HF; fixed dosing without plasma monitoring may produce subtherapeutic or supratherapeutic concentrations given the variability in oral bioavailability and metabolism across individuals.

8. Sourcing and Quality Verification

Omecamtiv mecarbil is not approved as a medicine in any jurisdiction as of the date of this monograph. Pharmaceutical-grade material is available only through clinical trial supply chains managed by Cytokinetics and its partners. Investigators requiring the compound for research applications must rely on research-grade chemical suppliers.

Research-grade omecamtiv mecarbil is available from multiple specialty chemical and pharmaceutical research suppliers (MedChemExpress [catalog HY-14233], Selleckchem [catalog S2623], Cayman Chemical, Tocris, Sigma-Aldrich/MilliporeSigma, BenchChem, and others) at greater than 98 percent purity by HPLC. Supply is in milligram to gram quantities as the free base or as the dihydrochloride salt. Pricing is moderate, in the range of \$50 to \$300 per 50 mg at the time of monograph preparation.

Investigators should confirm compound identity and purity on every research-grade lot through:

- High-performance liquid chromatography area-percent purity, ideally greater than 98 percent
- Mass spectrometry confirmation of molecular weight (402.19 for the protonated free base $[M+H]^+$, calculated from the monoisotopic mass of 401.1863)
- Nuclear magnetic resonance spectroscopy (1H and ^{13}C) for structural confirmation, with reference spectra available from PubChem and supplier certificates
- Karl Fischer or thermogravimetric analysis for residual water content
- Residual solvent analysis by gas chromatography

The molecular structure of omecamtiv mecarbil is well characterized and stable; counterfeit material is unlikely given the specificity of the compound class. However, lot-to-lot variability in purity and residual solvent content is observed among research-grade suppliers, and on-receipt analytical confirmation is appropriate for any investigation where dose-response precision is required.

9. Reconstitution and Handling

Omecamtiv mecarbil free base has limited aqueous solubility but is freely soluble in dimethyl sulfoxide (DMSO) at concentrations exceeding 50 mM. The dihydrochloride salt has improved aqueous solubility suitable for biological assays.

For in vitro research applications, stock solutions are typically prepared at 10 to 50 mM in DMSO and stored at -20 degrees Celsius in single-use aliquots. Working concentrations for in vitro cardiomyocyte studies range from 0.03 to 1.0 micromolar, with 0.1 to 0.5 micromolar representing the range at which force enhancement is observed without excessive relaxation impairment [13, 28]. The final DMSO concentration in cell culture or physiological buffer should be maintained below 0.1 percent (v/v) to avoid solvent effects on cardiomyocyte function.

For parenteral research formulations, the dihydrochloride salt can be dissolved in sterile water for injection or normal saline. The compound is chemically stable under refrigerated conditions (2 to 8 degrees Celsius) in both solid and solution forms.

Storage recommendations: lyophilized or crystalline powder at -20 degrees Celsius, protected from light and moisture. DMSO stock solutions are stable for at least 6 months at -20 degrees Celsius in sealed, desiccated containers. Aqueous solutions should be used within 24 hours of preparation or stored as frozen aliquots for up to 4 weeks. Minimize freeze-thaw cycles.

For skinned fiber or myofibril preparations, omecamtiv mecarbil is dissolved directly in relaxing or activating buffer at the desired final concentration (typically 0.1 to 1.0 micromolar for functional assays) [13].

10. Stack Interaction Considerations

Omecamtiv mecarbil interacts with several drug classes through its metabolic profile and its unique mechanism of cardiac contractility enhancement. Investigators conducting research with omecamtiv mecarbil, particularly in combination with other cardiovascular research compounds, should consider the following interactions.

CYP3A4 inhibitors: Strong CYP3A4 inhibitors (ketoconazole, itraconazole, ritonavir, clarithromycin) increase omecamtiv mecarbil exposure by approximately 50 percent in CYP2D6 extensive metabolizers [20]. Moderate CYP3A4 inhibitors (diltiazem, verapamil, erythromycin) produce smaller effects. Dose adjustment may be warranted in combination studies.

CYP3A4 inducers: Strong inducers (rifampin, carbamazepine, phenytoin, phenobarbital) are expected to reduce omecamtiv mecarbil exposure through increased CYP4 and CYP3A4 metabolism, though formal interaction studies with strong inducers have not been published. Omecamtiv mecarbil itself showed minimal CYP3A4 induction potential (18 percent decrease in midazolam AUC) [20].

Proton pump inhibitors: Omeprazole did not meaningfully alter omecamtiv mecarbil pharmacokinetics [27], indicating that gastric pH does not affect absorption.

Beta-adrenergic blockers: In GALACTIC-HF, 87 percent of patients were receiving beta-blockers at baseline [18]. The combination was well tolerated, and the omecamtiv mecarbil treatment effect was preserved regardless of beta-blocker use. The mechanistic complementarity is logical: beta-blockers reduce heart rate and neurohormonal activation while omecamtiv mecarbil directly enhances systolic function without stimulating adrenergic signaling.

Angiotensin receptor-neprilysin inhibitors (ARNI): Approximately 19 percent of GALACTIC-HF patients received sacubitril/valsartan at baseline [18]. The treatment benefit of omecamtiv mecarbil was preserved in this subgroup, supporting mechanistic complementarity between neurohormonal modulation and sarcomere-level contractility enhancement.

Conventional inotropes (dobutamine, milrinone): Omecamtiv mecarbil acts through a fundamentally different mechanism from catecholamine-based and phosphodiesterase III-based inotropes. Combination with dobutamine has been evaluated in preclinical cardiac slice preparations without evidence of excessive contractility enhancement [29]. However, additive prolongation of systolic ejection time could theoretically compromise diastolic filling at high combined concentrations. This combination has not been systematically studied in human research.

Calcium sensitizers (levosimendan): Levosimendan sensitizes troponin C to calcium, whereas omecamtiv mecarbil activates myosin directly. The two mechanisms are pharmacologically distinct and potentially complementary, though no human combination data exist. In isolated cardiomyocytes, levosimendan accelerated contraction and relaxation kinetics, in contrast to the relaxation impairment observed with omecamtiv mecarbil [28].

QT-prolonging agents: Omecamtiv mecarbil does not prolong the QTc interval [23]; no additive QT risk is expected in combination with QT-prolonging medications.

Cardiac glycosides (digoxin): The combination with digoxin has not been formally studied. Both classes increase myocardial contractility, but through different mechanisms (Na⁺/K⁺-ATPase inhibition vs myosin activation). Additive inotropy is theoretically plausible.

11. Adverse Events and Safety

11.1 Common adverse events

The adverse event profile of omecamtiv mecarbil in controlled clinical trials is notable for the absence of the classical inotrope toxicity signals (tachycardia, hypotension, arrhythmia). In GALACTIC-HF, with nearly 7,500 patient-years of follow-up, there were no significant differences between omecamtiv mecarbil and placebo in the incidence of myocardial ischemia, ventricular arrhythmias, or death [18]. No detrimental effects on blood pressure, heart rate, serum creatinine, or potassium were observed [18]. The safety profile was consistent across subgroups defined by age, ejection fraction, blood pressure, and background therapy [18, 19, 26].

In METEORIC-HF, serious adverse events occurred in 16.2 percent of the omecamtiv mecarbil group versus 14.3 percent of the placebo group, with low and balanced rates of death (1.6% vs 1.1%), dizziness (4.9% vs 5.5%), and fatigue (4.9% vs 4.4%) [25].

11.2 Troponin elevation

The most discussed safety signal is a modest, concentration-related elevation in cardiac troponin I (cTnI). In COSMIC-HF, the median change from baseline at week 20 was 0.001 ng/mL in the fixed-dose group and 0.006 ng/mL in the PK-titration group compared with placebo; none were judged due to myocardial ischemia or infarction [10, 15]. In ATOMIC-AHF, troponin concentrations were modestly higher in omecamtiv mecarbil-treated patients (median difference 0.004 ng/mL at 48 hours) without a clear concentration-response relationship [9].

In GALACTIC-HF, a dedicated troponin analysis by Felker et al. (2024) reported that omecamtiv mecarbil produced a modest cTnI increase that was related to plasma drug concentrations and peaked at 6 weeks [30]. Critically, there was no differential effect of omecamtiv mecarbil on either safety or efficacy based on baseline cTnI status or change in cTnI, and the increase did not translate into excess cardiac ischemic events [30]. The mechanism of the troponin elevation is attributed to increased cardiomyocyte mechanical work and sarcomere turnover rather than myocardial injury.

11.3 Myocardial ischemia at supratherapeutic concentrations

In the first-in-human study, the dose-limiting toxicity was myocardial ischemia due to excessive prolongation of systolic ejection time at the highest infusion rate (approaching 1.0 mg/kg/h) [3]. In the Phase 2a study, cardiac ischemia occurred in two patients at plasma concentrations of approximately 1750 and 1350 ng/mL [4]. The mechanism is diastolic in nature: excessive systolic ejection time encroaches on the diastolic filling period, reducing coronary perfusion time and myocardial oxygen delivery. This toxicity defines the upper boundary of the therapeutic window and was the rationale for PK-guided dose titration in Phase 2b and Phase 3 trials, targeting plasma concentrations of 200 to 600 ng/mL [10, 18].

11.4 QTc and arrhythmia

The thorough QT study demonstrated that omecamtiv mecarbil does not prolong the QTc interval at therapeutic concentrations, with an effect on ddQTcF exceeding 10 ms excluded up to plasma concentrations of approximately 800 ng/mL [23]. In GALACTIC-HF, there was no increase in ventricular or supraventricular tachyarrhythmias with omecamtiv mecarbil [18]. In ATOMIC-AHF, supraventricular tachyarrhythmias were numerically lower in the omecamtiv mecarbil group (3.6%) than in the placebo group (6.6%) [9].

11.5 Special safety considerations

No specific safety signals have been identified in subgroups defined by age, sex, race, diabetes status, or atrial fibrillation [18, 19]. The exercise safety study in patients with ischemic cardiomyopathy and angina reported that omecamtiv mecarbil was well tolerated during exercise testing, with no increase in exercise-induced angina [6]. Pregnancy data are not available; the compound has not been studied in pediatric populations.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five heart failure therapeutic agents against omecamtiv mecarbil, evaluated against five competency standards: novelty, effect size, promising potential, side-effect profile, and overall validation. The five comparators span the contemporary HFrEF treatment landscape and represent distinct mechanistic approaches to myocardial contractility or neurohormonal modulation.

12.1 Sacubitril/Valsartan (LCZ696, Entresto)

Mechanism: First-in-class angiotensin receptor-neprilysin inhibitor (ARNI) combining sacubitril (a prodrug whose active metabolite inhibits neprilysin) with valsartan (a selective angiotensin II type 1 receptor blocker). Neprilysin inhibition increases circulating natriuretic peptides, promoting vasodilation, natriuresis, and anti-remodeling effects [31]. The mechanism is neurohormonal, fundamentally distinct from the sarcomere-level contractility enhancement of omecamtiv mecarbil.

Development trajectory: The PARADIGM-HF trial randomized 8,442 patients with symptomatic chronic HFrEF (LVEF 40% or below) to sacubitril/valsartan or enalapril [31]. The trial was stopped early for overwhelming benefit after a median follow-up of 27 months. The FDA granted approval on July 7, 2015.

Clinical outcome: The primary composite of cardiovascular death or first HF hospitalization: HR 0.80 (95% CI 0.73 to 0.87; $p < 0.001$) [31]. Cardiovascular death: HR 0.80 (95% CI 0.71 to 0.89). All-cause mortality: HR 0.84 (95% CI 0.76 to 0.93) [31].

Comparison to omecamtiv mecarbil: The PARADIGM-HF HR of 0.80 is substantially more favorable than the GALACTIC-HF HR of 0.92 [18, 31]. However, the two agents are not direct competitors; sacubitril/valsartan is now foundational guideline-directed therapy, and omecamtiv mecarbil is positioned as an additive agent. In GALACTIC-HF, approximately 19% of patients received sacubitril/valsartan, and the treatment benefit of omecamtiv mecarbil was preserved in this subgroup [18].

Scores: Novelty: 4/5. Effect size: 5/5. Promising potential: 5/5. Side-effect profile: 3/5 (hypotension, hyperkalemia). Overall validation: 5/5.

12.2 Vericiguat (BAY 1021189, Verquvo)

Mechanism: Soluble guanylate cyclase (sGC) stimulator that directly stimulates sGC independently of nitric oxide and sensitizes sGC to endogenous NO, restoring impaired NO-sGC-cGMP signaling [32]. The mechanism is vascular and neurohormonal.

Development trajectory: The VICTORIA trial randomized 5,050 patients with chronic HFrEF (LVEF below 45%) and recent worsening heart failure to vericiguat or placebo [32]. FDA approval was granted January 20, 2021.

Clinical outcome: Primary composite of cardiovascular death or first HF hospitalization: HR 0.90 (95% CI 0.82 to 0.98; $p = 0.02$) [32]. Cardiovascular death alone: HR 0.93 (95% CI 0.81 to 1.06; not significant). All-cause mortality: HR 0.95 (95% CI 0.84 to 1.07; not significant) [32].

Comparison to omecamtiv mecarbil: Both agents demonstrated modest but significant reductions in the primary composite without significant effects on cardiovascular death alone [18, 32]. VICTORIA enrolled a higher-acuity population (recently worsened HF). Both agents are positioned as additive to background GDMT through entirely different mechanisms, and could theoretically be combined.

Scores: Novelty: 4/5. Effect size: 2/5. Promising potential: 4/5. Side-effect profile: 4/5 (symptomatic hypotension, anemia). Overall validation: 4/5.

12.3 Levosimendan (Simdax)

Mechanism: Calcium sensitizer and inodilator with triple mechanism: (1) selective binding to calcium-saturated cardiac troponin C enhancing myofilament force generation; (2) opening of ATP-sensitive potassium channels in vascular smooth muscle producing vasodilation; (3) modest phosphodiesterase III inhibition [34]. The troponin C mechanism enhances contractility calcium-dependently, mechanistically distinct from the myosin-level activation of omecamtiv mecarbil.

Development trajectory: The LIDO trial ($n = 203$) compared levosimendan with dobutamine in severe low-output heart failure and reported superior hemodynamic improvement (28% vs 15%, $p = 0.022$) and lower 6-month mortality (26% vs

38%, $p = 0.029$) [34]. The SURVIVE trial ($n = 1,327$) found no significant difference in 180-day all-cause mortality (26% vs 28%; HR 0.91; 95% CI 0.74 to 1.13; $p = 0.40$) [35]. Levosimendan is approved in 58 countries (primarily European markets) but has not been approved by the FDA.

Clinical outcome: Consistent hemodynamic improvement in acute decompensated HF, but mortality benefit not confirmed in the large SURVIVE trial [34, 35].

Comparison to omecamtiv mecarbil: Both agents enhance contractility without calcium overload, but through different sarcomeric targets (troponin C vs myosin). Levosimendan is an intravenous, short-duration agent for acute HF; omecamtiv mecarbil is an oral, chronic-use agent. The GALACTIC-HF HR of 0.92 represents a more rigorous outcomes demonstration than anything levosimendan has produced in large-scale trials [18, 35].

Scores: Novelty: 3/5. Effect size: 3/5 (hemodynamic large; mortality neutral). Promising potential: 2/5 (no FDA path). Side-effect profile: 2/5 (hypotension, atrial arrhythmia). Overall validation: 3/5.

12.4 Danicamtiv (MYK-491)

Mechanism: Selective allosteric activator of cardiac myosin (MYH7), elevating ATPase turnover rate by approximately 85 percent in ventricular myofibrils and increasing calcium sensitivity of force production [37]. The closest mechanistic comparator to omecamtiv mecarbil.

Development trajectory: MyoKardia (acquired by Bristol-Myers Squibb in 2020) advanced danicamtiv through a Phase 2a randomized, double-blind, placebo-controlled trial in 40 patients with stable HFrEF (mean LVEF 32%), testing 50 to 100 mg twice daily for 7 days [37]. Significant improvements were reported in stroke volume (+7.8 mL at medium plasma concentrations; $p < 0.01$), systolic ejection time (+36 ms; $p < 0.01$), global longitudinal strain, and global circumferential strain [37]. Troponin elevations occurred in 23 percent of danicamtiv patients versus 0 percent placebo [37]. Bristol-Myers Squibb terminated the development program in February 2024 due to a change in business objectives.

Comparison to omecamtiv mecarbil: Both share the cardiac myosin activator mechanism. Omecamtiv mecarbil is vastly more clinically validated: GALACTIC-HF ($n = 8,256$, positive outcomes endpoint) versus a single Phase 2a study ($n = 40$, surro-

gate endpoints) [18, 37]. The termination of danicamtiv leaves omecamtiv mecarbil as the sole cardiac myosin activator with advanced outcomes data.

Scores: Novelty: 4/5 (shared class). Effect size: 2/5 (surrogate only). Promising potential: 1/5 (terminated). Side-effect profile: 3/5 (troponin 23%). Overall validation: 2/5.

12.5 Istaroxime (PST-2744)

Mechanism: First-in-class dual-mechanism inotropic and lusitropic agent combining inhibition of sarcolemmal Na⁺/K⁺-ATPase (positive inotropy) with stimulation of SERCA2a (positive lusitropy, accelerating diastolic calcium reuptake) [36]. This dual mechanism addresses both systolic and diastolic dysfunction simultaneously.

Development trajectory: The HORIZON-HF trial (n = 120) evaluated intravenous istaroxime at 0.5, 1.0, and 1.5 micrograms/kg/min over 6 hours in acute HF patients with LVEF 35 percent or below [36]. All three doses lowered pulmonary capillary wedge pressure by 3 to 5 mmHg, decreased diastolic stiffness, and increased E-prime velocity [36]. The SEISMic Phase 2b study in patients with early cardiogenic shock showed significant systolic blood pressure improvement (62.0 +/- 7 vs 36.4 +/- 7 mmHg*h; p = 0.007) and robust hemodynamic effects. Istaroxime is currently in Phase 2b with a Phase 3 path initiated.

Comparison to omecamtiv mecarbil: Istaroxime is an intravenous agent for acute HF and cardiogenic shock; omecamtiv mecarbil is an oral agent for chronic HFrEF. Omecamtiv mecarbil's GALACTIC-HF outcomes data (n = 8,256) represent far more advanced clinical validation than istaroxime's Phase 2b hemodynamic endpoints [18, 36]. Istaroxime's unique lusitropic mechanism addresses diastolic dysfunction in a manner that omecamtiv mecarbil does not.

Scores: Novelty: 5/5. Effect size: 3/5 (hemodynamic robust; no outcomes data). Promising potential: 3/5 (Phase 2b positive). Side-effect profile: 2/5 (GI events, nausea). Overall validation: 2/5.

12.6 Comparator summary

The five compounds occupy distinct positions in the HFrEF pharmacology space. **Sacubitril/valsartan** is the most clinically validated agent with a 20 percent relative risk reduction, regulatory approval worldwide, and guideline-directed first-line sta-

tus [31]. **Vericiguat** addresses worsening HF with a modest 10 percent risk reduction through sGC stimulation [32]. **Levosimendan** provides reliable hemodynamic improvement in acute HF but has failed to demonstrate consistent mortality benefit [34, 35]. **Danicamtiv**, the closest mechanistic analog, produced promising Phase 2a echocardiographic data but was terminated before outcomes testing [37]. **Istaroxime** presents a novel dual inotropic-lusitropic mechanism but remains in early clinical development [36].

Omecamtiv mecarbil occupies a unique position: it is the only selective cardiac myosin activator with a completed Phase 3 outcomes trial demonstrating a positive primary endpoint (GALACTIC-HF: HR 0.92 in 8,256 patients) [18]. It is the only oral, chronically administered agent that directly enhances cardiac sarcomere function without raising intracellular calcium or increasing myocardial oxygen consumption. The GALACTIC-HF subgroup analyses identify the sickest patients (lowest EF, highest NT-proBNP, lowest blood pressure) as those most likely to benefit [19, 24, 26], a profile not shared by the neurohormonal agents. The principal limitation relative to sacubitril/valsartan and vericiguat is the absence of a significant effect on cardiovascular death (HR 1.01), which constrains the strength of the outcome signal and has delayed regulatory approval [18]. The ongoing COMET-HF trial, enriched for patients with LVEF below 30 percent, will determine whether the subgroup-enriched population demonstrates a benefit-risk profile sufficient for registration.

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