

COEURative

**Revolutionary Therapy for Refractory Angina
in Coronary Artery Disease**

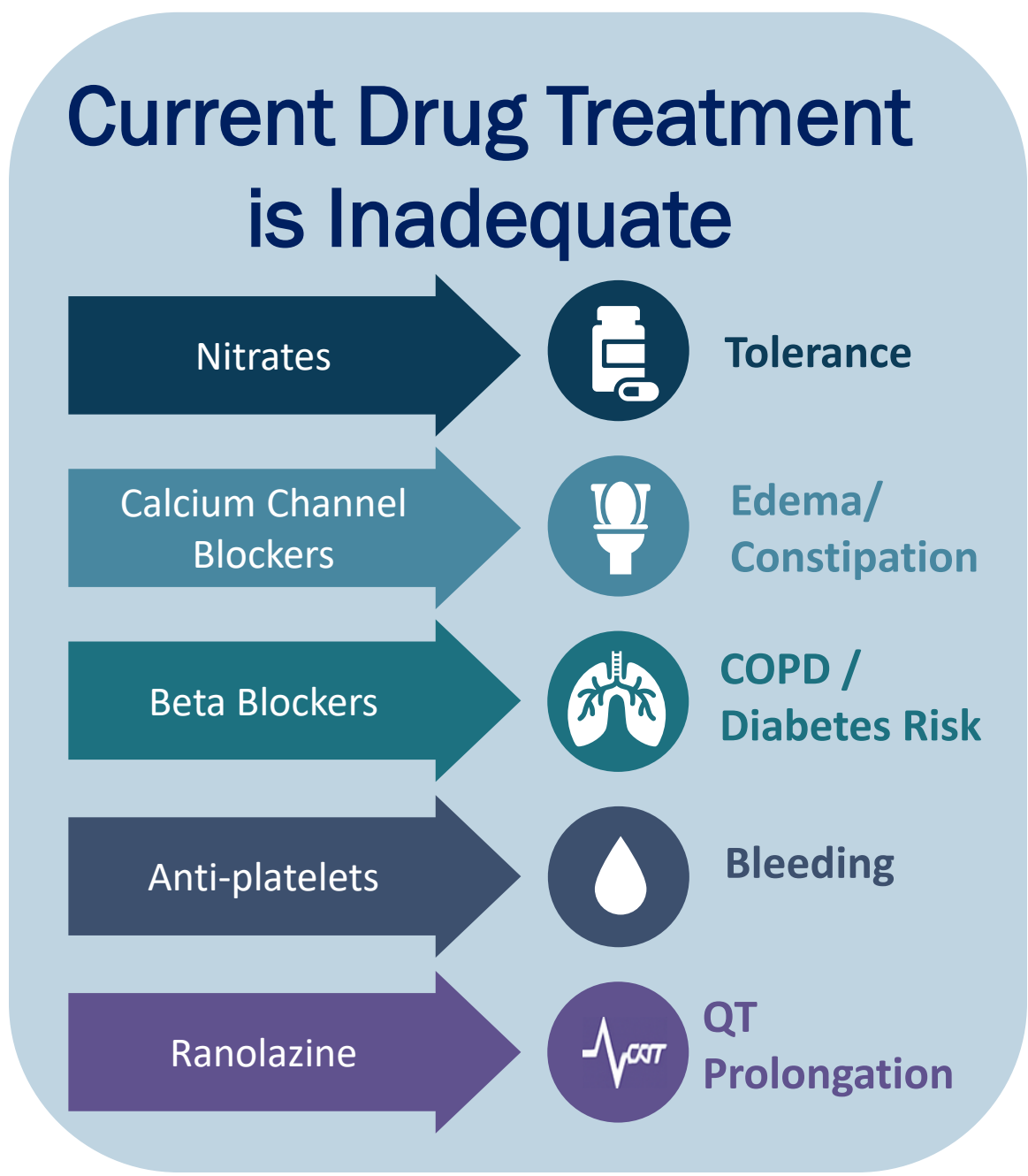
**John F. Schmedtje Jr., MD
Roanoke, Virginia**

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Coronary Artery Disease /Angina Pectoris

The Pharmaceutical Standard of Care for Angina has Severe Limitations & Gaps

A New Treatment for Angina Pectoris
Represents a Significant Opportunity Within
\$16 Billion Global Market by 2029



11 million
Angina patients
in US

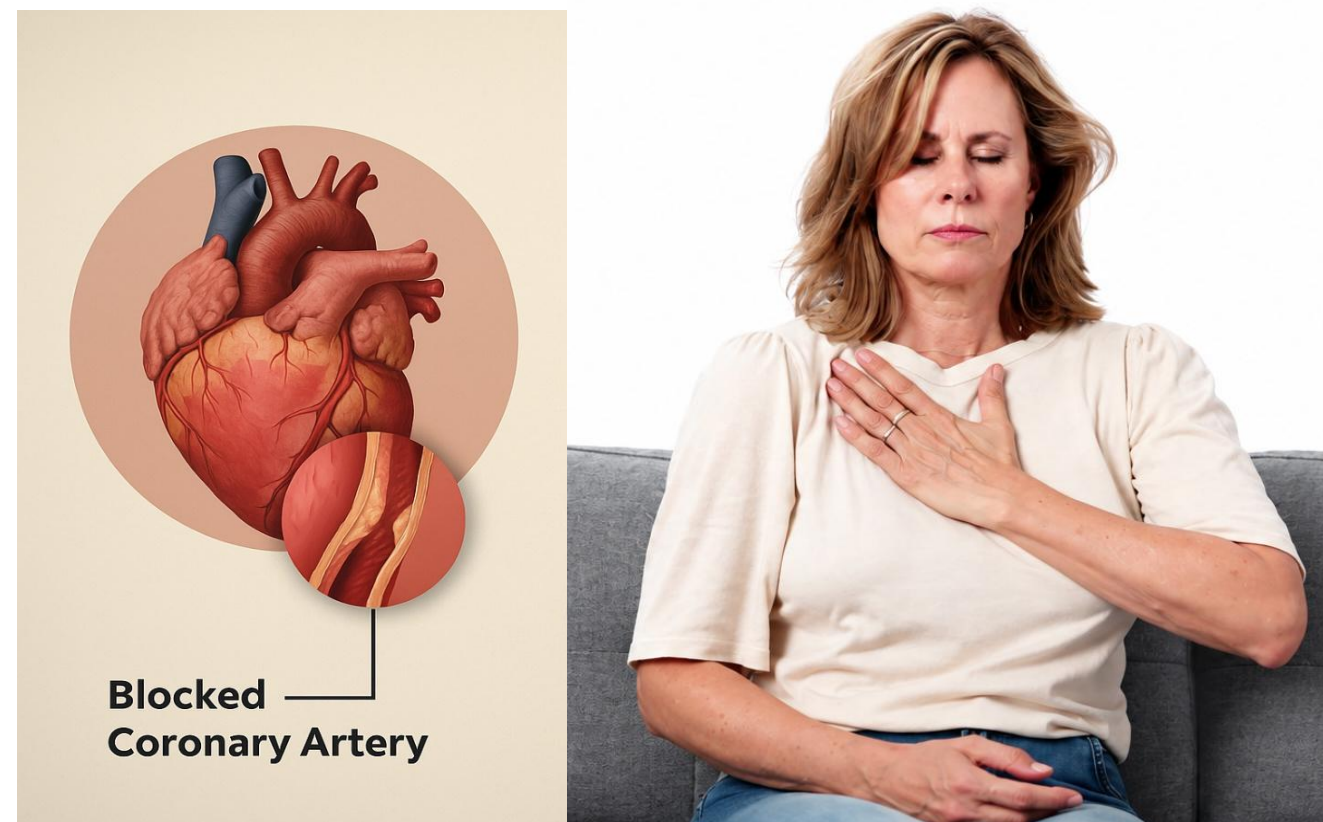
1 Million
Refractory Angina
patients in US

3 million
with **INOCA**

Annual mortality
3% to 17%

Millions of Patients Need More Than CABG/PCI/EECP: New Drugs are Needed

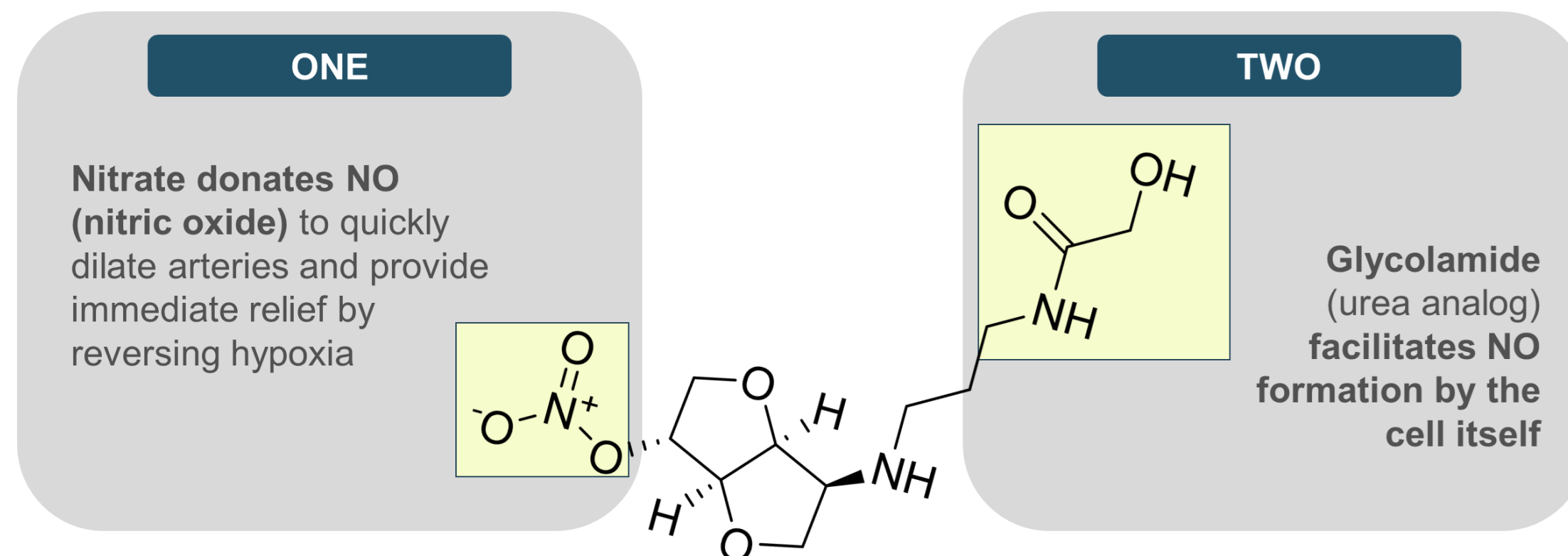
Our Solution Features A Dual-Action Mechanism: *Not Just Another Nitrate*



Hypoxia: A Target in Refractory Angina and INOCA

- Hypoxia and inflammation in heart diseases with different etiologies may be reversed by the same molecule: Nitric Oxide (NO), released by Nitroglycerin and Isosorbide Nitrates
- Hypoxic induction of the urea transporter is another target for experimental therapeutics
- **Refractory Angina**: Found in 1 million of the 11 million US patients with angina with incidence of up to 100,000 per year
- **INOCA**: Half of patients with demonstrable myocardial ischemia have no angiographic obstructive epicardial coronary stenosis; prevalence in US of 3 million, mainly women

CR-0305 is Designed to Deliver a ONE-TWO Punch



CR-0305 uniquely offers both immediate vasodilation (rapid NO donation) and potential long-term vascular benefit (cellular NO upregulation)

Glycolamide moiety for extended action → potentially targets hypoxic vessels

Preclinical data: CR-0305 likely provides durable and superior vasodilation to gold-standard agents and may provide a SELECTIVE effect where hypoxia exists

Schmedtje et al. Biomed. Pharmacother. 2024;173:116378.

CR-0305 Is The Intellectual Property of Coeurative, Inc.

- **Composition of matter and cardiovascular methods are covered by US Patents no. 10501471 and US Patent no. 10,913,748. which expire in 2039 at this time.**
- **The IP in these two US patents are found in International Patent Cooperation Treaty Application PCT/US2019/058241, which has been through National Phase applications.**
- **Patents have been granted by Australia, Canada, China, European Union (EU Unitary Patent and Czechia, Ireland, Spain and Switzerland), India, Israel, Japan, and Mexico. The national phase application in Canada is pending.**
- **All patents discussed herein are assigned to Coeurative, Inc.**

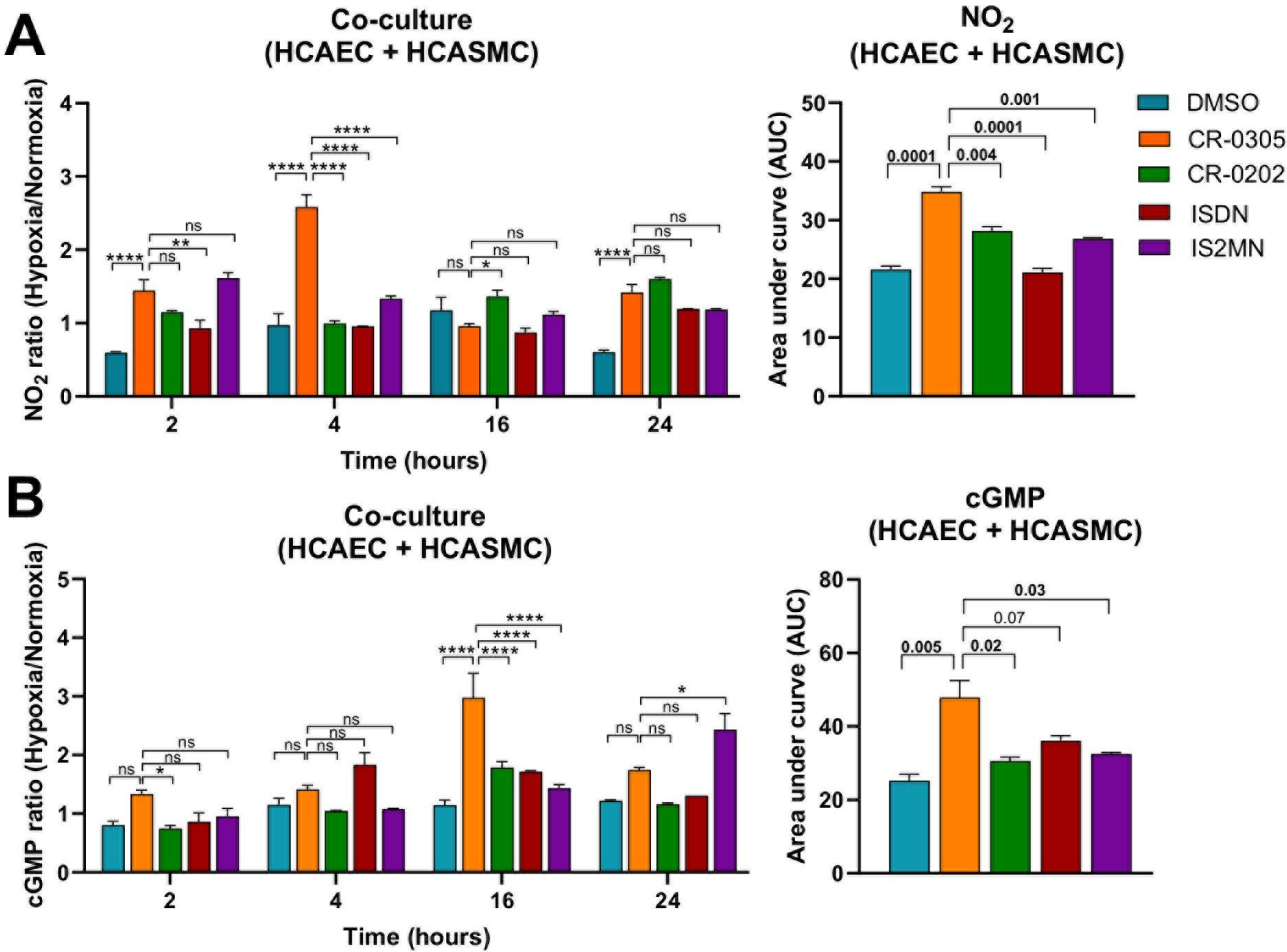
Jurisdiction	Number	Filing Date	Granted Date
United States	10,501,471	2-Jun-19	10-Dec-19
United States	10,913,748	12-Oct-19	9-Feb-21
PCT	US2019/058241	27-Oct-19	National Phases
EU Unitary Patent	EP3873457	27-Oct-19	7-Feb-24
Czechia	EP3873457	27-Oct-19	7-Feb-24
Ireland	EP3873457	27-Oct-19	7-Feb-24
Spain	EP3873457	27-Oct-19	18-Mar-24
Switzerland	EP3873457	27-Oct-19	7-Feb-24
Australia	2019373199	27-Oct-19	30-Jan-25
Israel	282703	27-Oct-19	2-Apr-24
India	473595	27-Oct-19	28-Nov-23
Japan	7452881	27-Oct-19	11-Mar-24
Mexico	410514	27-Oct-19	14-Feb-24
China	ZL201980065702.9	27-Oct-19	23-Jun-26
Canada (pending)	3,115,113	27-Oct-19	Pending

CR-0305 Boosts Key Vasodilatory Biomarkers in Cellular Hypoxia *In Vitro* Using *New Approach Methodology*

New Approach Methodology:
Application of CR-0305 to human (HCAEC/HCAEMC) cell cultures grown under low-oxygen (hypoxic) conditions produced a significant increase in nitric oxide metabolite (NO₂) and cyclic GMP (cGMP) biomarkers compared with normoxia

A) CR-0305 significantly raised the hypoxia/normoxia ratio of NO₂ over time. Two-way ANOVA with Tukey post-hoc was used to assess statistically significant differences: * p<0.05; ** p<0.01; *** p<0.001; **** p<0.0001. Area-under-curve (AUC) analysis confirmed robust and statistically significant induction compared to control, p values listed.

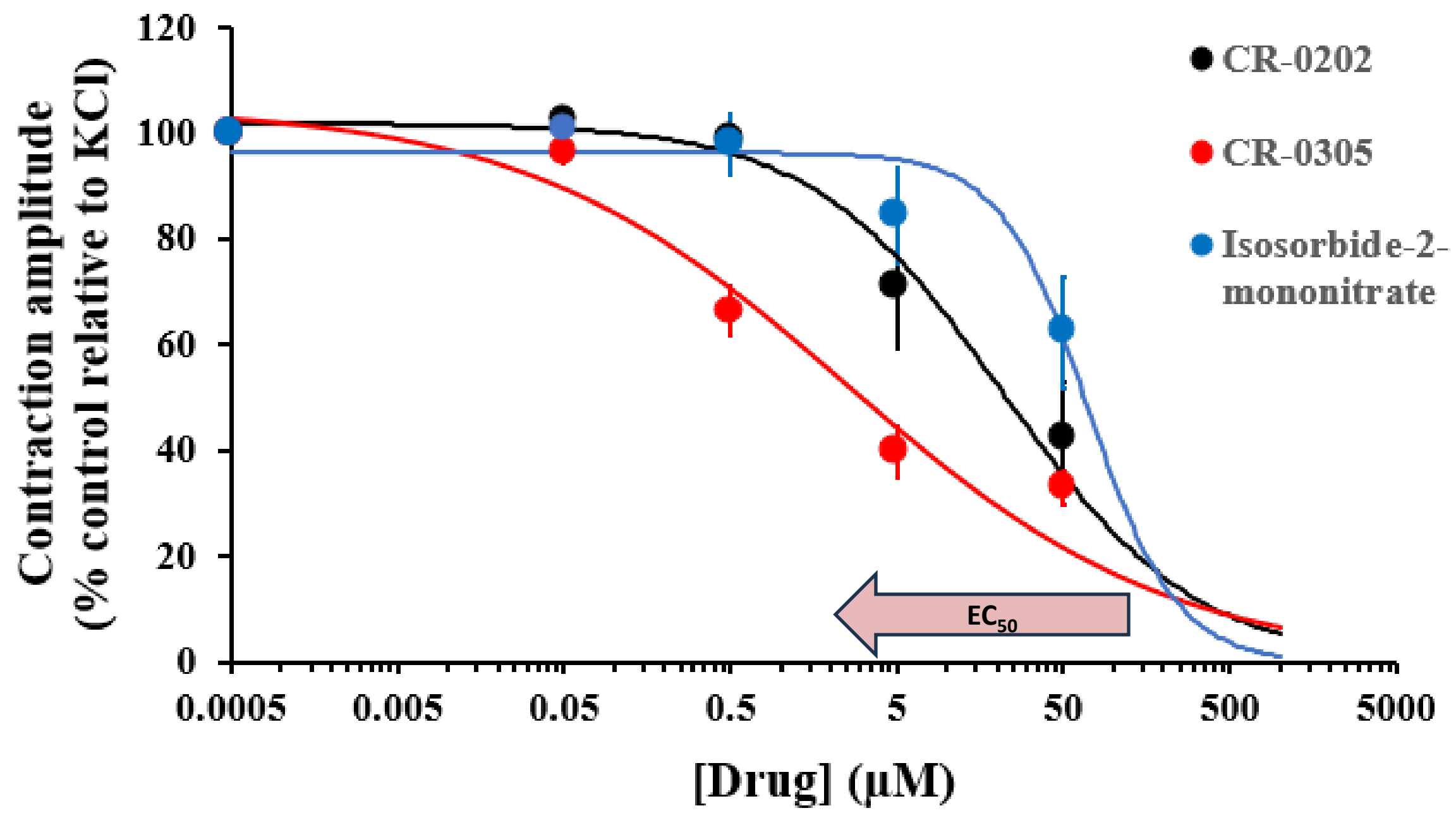
B) Co-culture cell lysates revealed strongly elevated cGMP production, mirroring the NO₂ increase and highlighting CR-0305's powerful dual effect on endothelial function.



CR-0305 Demonstrates Higher Potency than Isosorbide Mononitrate in Relaxation of Human Coronary Arteries *Ex Vivo*

In human coronary arteries *ex vivo*, direct comparison of CR-0305 with a SOC organic nitrate after pre-contraction demonstrates vasorelaxation at much lower concentrations than isosorbide mononitrate

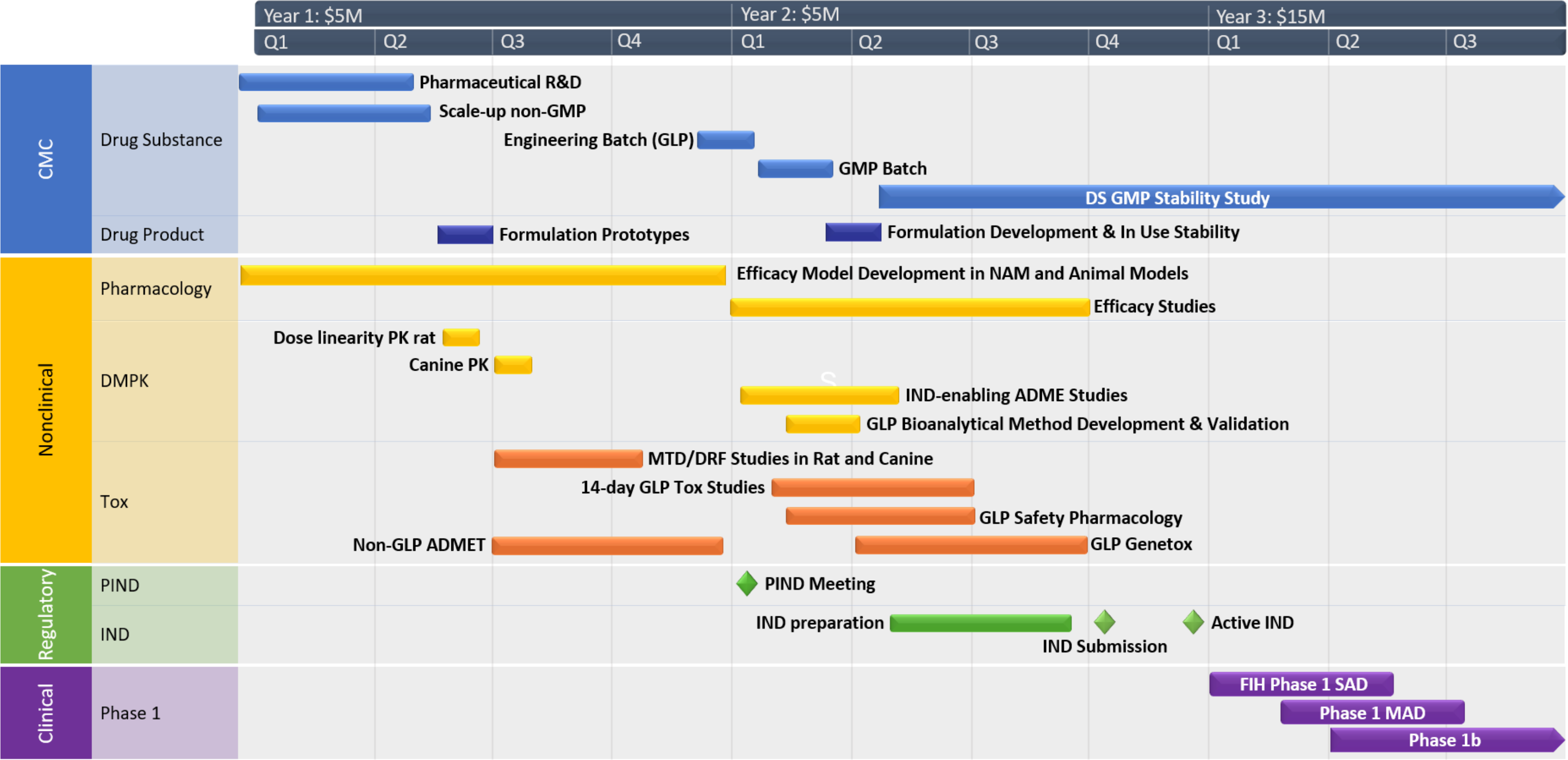
Specifically, CR-0305 achieves half-maximal relaxation (EC_{50}) at **3.0 μ M**, vs. **67.8 μ M** for isosorbide mononitrate—making CR-0305 over 20 times more potent. The superior potency suggests the potential to deliver more consistent, effective relief for patients who fail current nitrate therapies.



CR-0305 ADME/Tox and Safety Highlights

- ✓ **CR-0305 is highly soluble in simulated intestinal fluids**
- ✓ **Caco-2 cell monolayers treated with CR-0305 showed limited permeability, with passive diffusion and low efflux.**
-CR-0305 is not a substrate for active transport.
- ✓ **CR-0305 had 39% oral bioavailability with peak 0.6 µg/ml or roughly 2 µM**
-Effective plasma concentration of IS2MN in humans is 0.4 µg/ml
- ✓ **Of the seven major CYP isoforms tested, only CYP2D6 was significantly inhibited by 10 µM CR-0305.**
-CYP2D6 is a polymorphic metabolic enzyme of xenobiotics.
- ✓ **CR-0305 was not cytotoxic in immortalized human vascular endothelial cells (HMEC-1)**
-As determined by Cell TiterGlo assay of ATP production.
- ✓ **Mitochondrial testing revealed no evidence of toxicity or mitochondrial dysfunction with CR-0305**
-Using HMEC-1 and bovine mitochondria at concentrations up to the maximum tested dose of 10 µM.

CR-0305 Early Development Timeline with Budgeted Extramural Investments
Predicated on Availability of Operating Capital



Founder and CEO: John F. Schmedtje Jr.

- MD, 1981: Graduate of Honors Program in Medical Education at Northwestern University
- MPH, 1983: Harvard School of Public Health
- Internal Medicine Residency, 1986: Baylor College of Medicine
- Cardiology Fellowship, 1991: Medical College of Virginia
- Cardiology Faculty appointments at Baylor, University of Texas Medical Branch, Wake Forest University School of Medicine
- Published on hypoxia and vascular endothelium as lead or senior author in medical science journals with high impact factors such as Circulation Research and Journal of Biological Chemistry
- Winner of the 1996 Cournand & Comroe Young Investigator Prize from the American Heart Association for Cardiopulmonary Research
- Board Certified in Internal Medicine, Cardiovascular Disease and Nuclear Cardiology
- Team player with a 35-year track record of collaboration with the pharmaceutical industry on clinical trials and drug development
- Implementing Coeurative team and governance plan in 2027



Company Overview - First-in-class therapy for refractory angina pectoris

Urgent Unmet Medical Need

- Angina pectoris afflicts 11 million Americans, with 21% of patients still suffering monthly attacks despite medical therapy. One million patients in the US have the more serious refractory angina, with up to 100,000 new cases each year and annual mortality up to 17%.
- INOCA (ischemia with non-obstructive coronary arteries) patients are mainly women, and prevalence is estimated at 3 million in the US. Prognosis is like that of patients with single vessel obstructive disease, but there is no option for mechanical revascularization.
- Mechanical revascularization is rarely sufficient long term, and existing drug options such as calcium channel blockers, beta-blockers, anti-platelets, nitrates are hampered by insufficient efficacy, frequent tolerance, and significant side effects, leaving a large underserved population.

Lead Asset: CR-0305 - Innovative Dual-Mechanism Solution

- CR-0305 delivers a “one-two punch”: rapid vasodilation via nitric oxide (NO) donation and sustained benefit by modulating coronary smooth muscle relaxation to achieve targeted relief in hypoxic coronary arteries.
- Designed to overcome tachyphylaxis (tolerance) by addressing multiple pathways, CR-0305 aims to provide both fast-acting and durable control of angina symptoms.

Strong Preclinical Data & IP Protection

- CR-0305 exhibits 23× greater vasodilatory potency than isosorbide mononitrate (IC_{50} 3.0 μ M vs. 67.8 μ M) in human coronary artery ex vivo, with significant improvements in NO and cGMP generation using NAM in vitro.
- CR-0305 demonstrates low toxicity in human cell studies and secured IP protection, priority date 2019, with US and global patents granted.

Clear Path to In Vivo Efficacy and First-in-Human Trials

- Over \$1.9M secured from NIH SBIR, Virginia CCF, and private investors to date.
- Presently seeking \$5M for ADME-Tox work, NAM proof of concept and scale-up of API synthesis with in vivo and ex vivo demonstrations of efficacy, durability of effect, and selectivity, leading to pre-IND meeting with the FDA.
- Subsequently \$20M to complete IND-enabling studies, file IND, and launch first-in-human Phase 1 clinical trials of oral CR-0305 with treadmill testing in Phase 1b clinical trials—unlocking key value inflection point.



COEURative

OPENING HEARTS

A Management Strategy for Coronary Artery Disease with CR-0305

Visit: www.coeurative.com

Contact: jfs@coeurative.com