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CR-0305: Developing a Dual-Mechanism Therapy for Refractory Angina Pectoris and ANOCA

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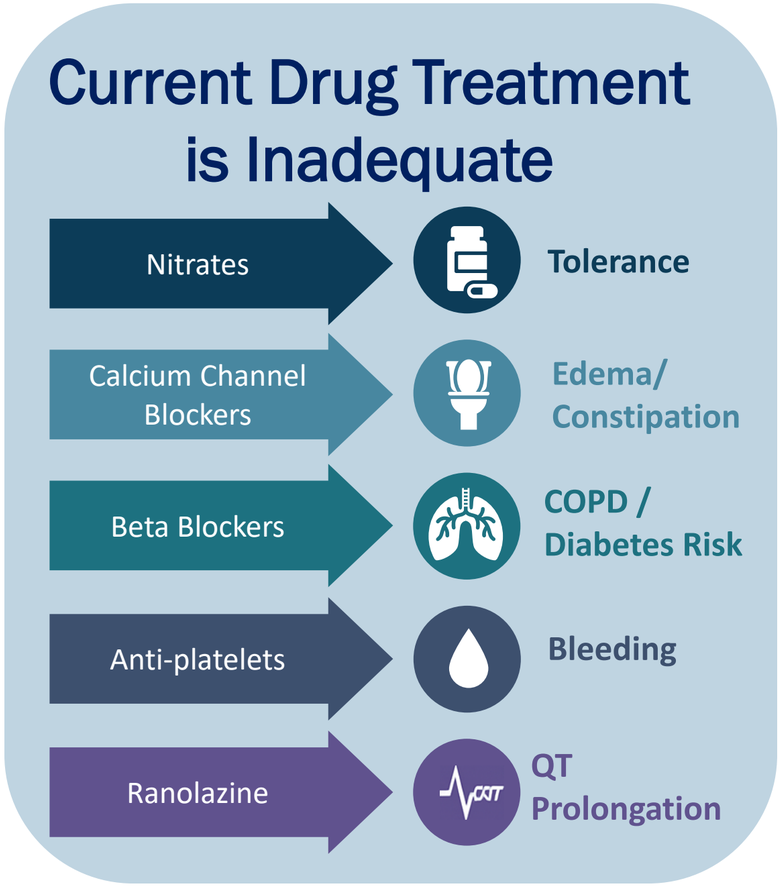
Coronary Artery Disease /Angina Pectoris: The Unmet Need In **Refractory Angina** and **ANOCA** (Angina with Non-Obstructive Coronary Arteries)



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

16 million
U.S. patients with CAD

900,000
U.S. patients with Refractory Angina

3 million
U.S. patients with ANOCA

Annual mortality
3% to 17%

Patients remain symptomatic despite medical therapy and revascularization options

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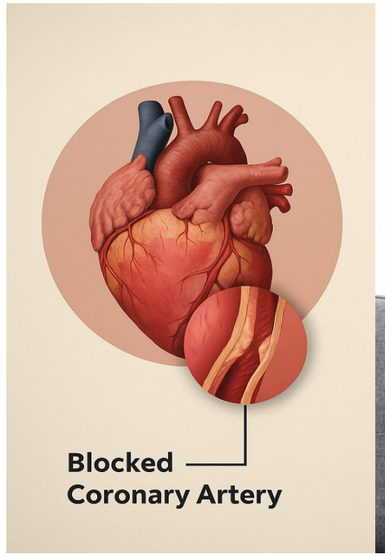
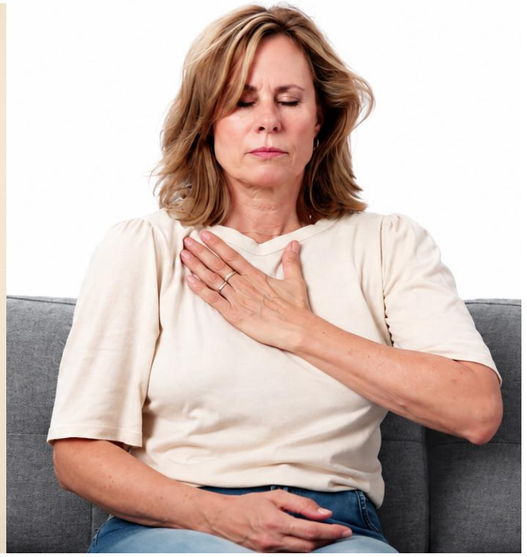
CR-0305 Combines NO with a Potential Second Mechanism of Vasodilatation





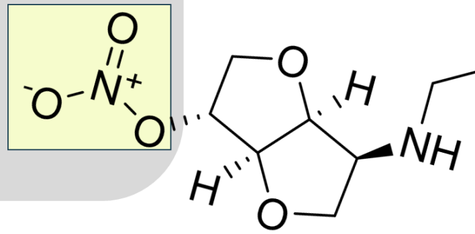
Hypoxia: A Target in <u>Refractory Angina</u> and <u>ANOCA</u>

- **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**
- **<u>Refractory Angina:</u> Found in 900,000 US patients with angina with incidence of up to 75,000 per year**
- **<u>ANOCA</u>: Half of patients with demonstrable myocardial ischemia have no angiographic obstructive epicardial coronary stenosis; prevalence in US of 3 million, majority women**

CR-0305 Dual Mechanism Design

ONE

Nitrate donates NO (nitric oxide) to quickly dilate arteries and provide immediate relief by reversing hypoxia



TWO

Glycolamide (urea analog) **facilitates NO formation by the cell itself**

CR-0305 is designed to combine rapid NO-mediated vasodilation with increased cellular NO signaling under hypoxic conditions

Glycolamide moiety is being investigated for sustained activity and preferential effects under hypoxic conditions

Preclinical studies support potential vasodilatory activity and motivate further evaluation of durability and hypoxia selectivity

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

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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, with exclusivity to 2044 pending NDA**
- **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

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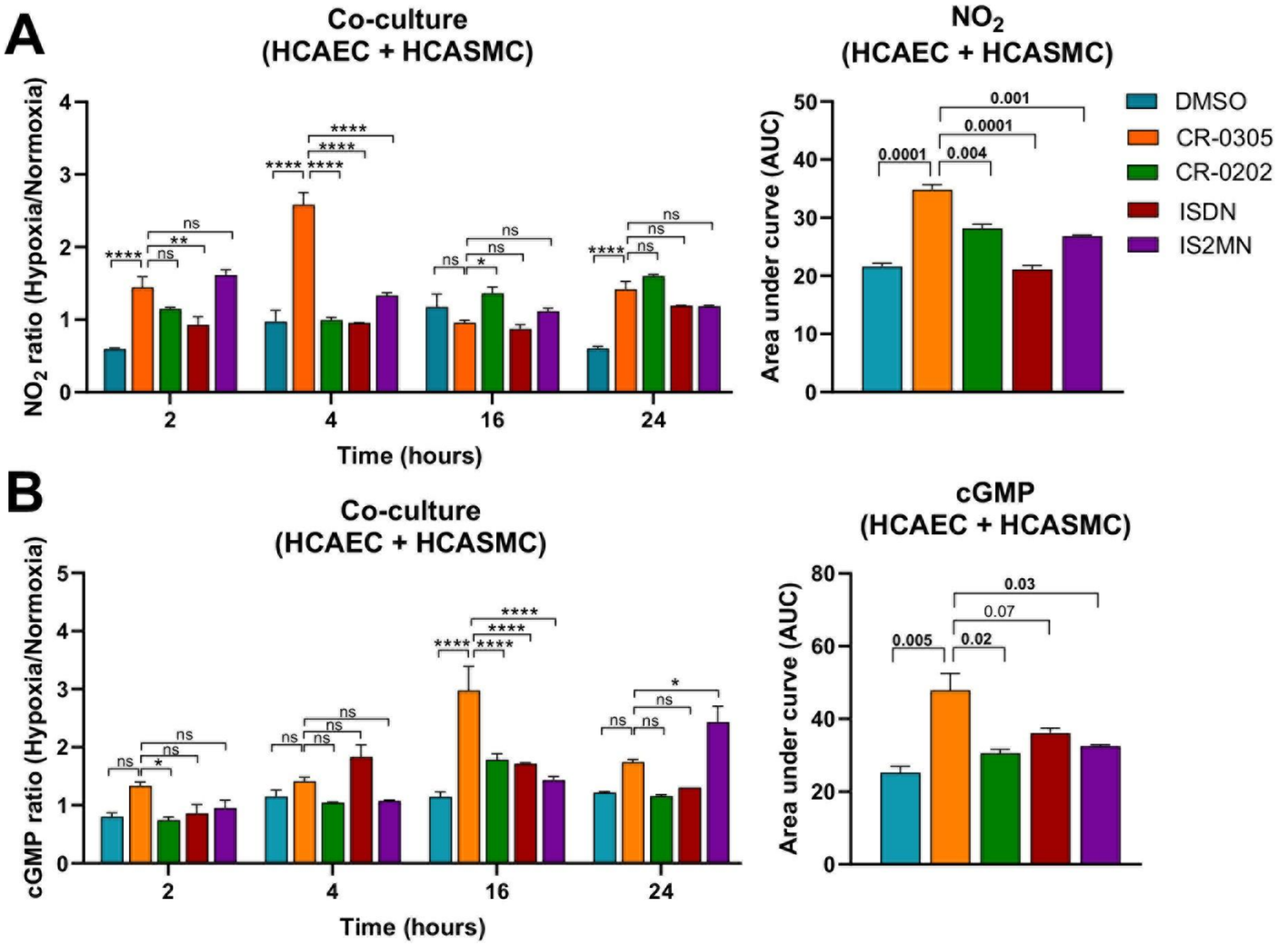
CR-0305 Increases NO_2 and cGMP in a Hypoxic Human Coronary Cell Co-culture

New Approach Methodology:
Application of CR-0305 to human (HCAEC/HCASMC) cell cultures grown under low-oxygen (hypoxic) conditions produced a significant increase in nitric oxide metabolite (NO_2) and cyclic GMP (cGMP) biomarkers compared with normoxia

A) CR-0305 significantly raised the hypoxia/normoxia ratio of NO_2 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 NO_2 increase and highlighting CR-0305's powerful dual effect on endothelial function.



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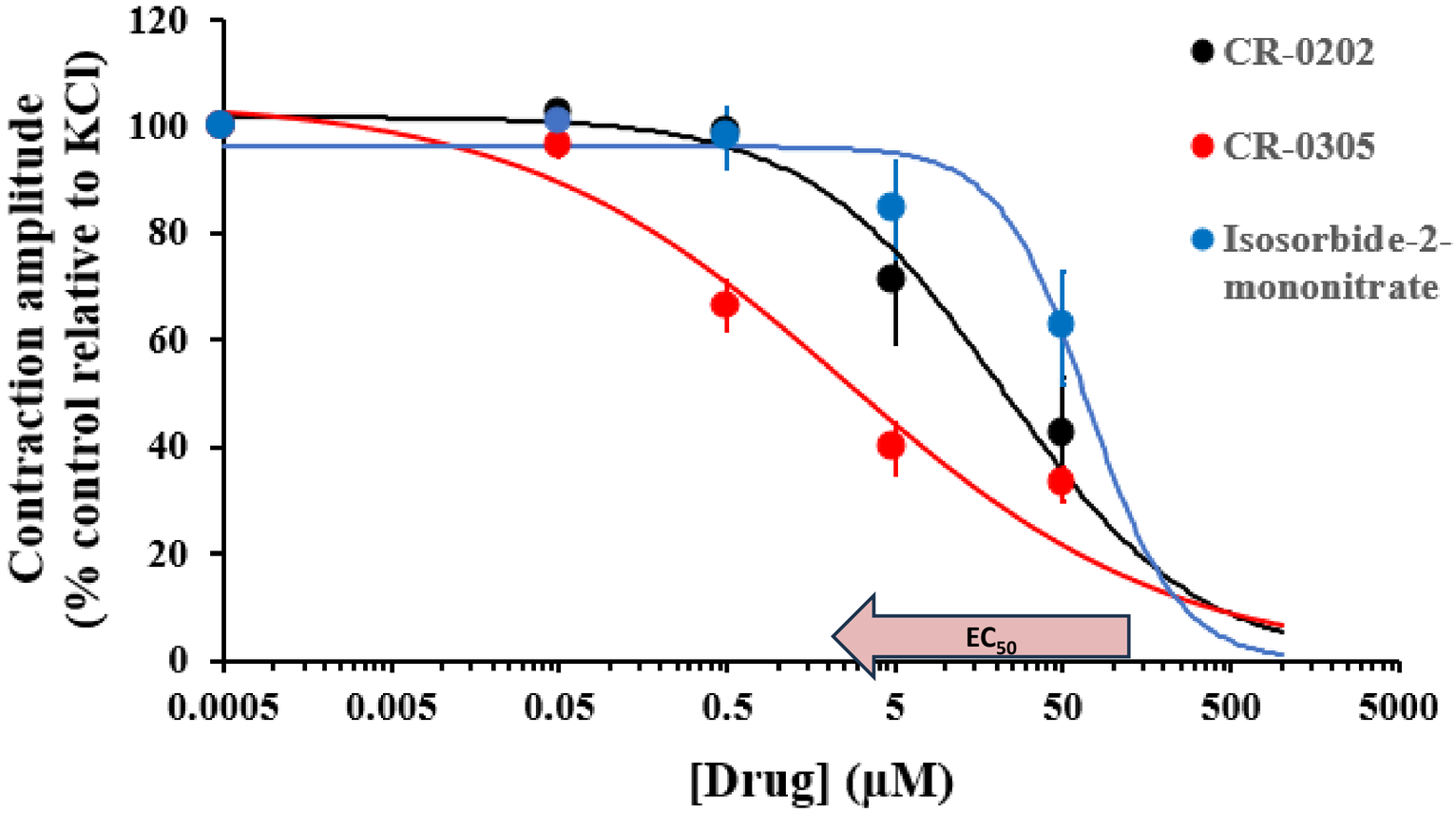
CR-0305 Demonstrates Higher Potency than Isosorbide Mononitrate in Relaxation of Human Coronary Arteries *Ex Vivo*

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 **3.0µM**, vs. **67.8µM** 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.



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Early ADME and *In Vitro* Safety Studies Support Continued Development of CR-0305

- ✓ **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**
- ✓ **No reduction in HMEC-1 viability was detected by ATP-based CellTiter-Glo assay under the tested conditions**
  - **-Using immortalized human vascular endothelial cells (HMEC-1)**
- ✓ **No mitochondrial toxicity or dysfunction was detected under the tested conditions with CR-0305**
  - **-Using HMEC-1 and bovine mitochondria at concentrations up to the maximum tested dose of 10 μM**

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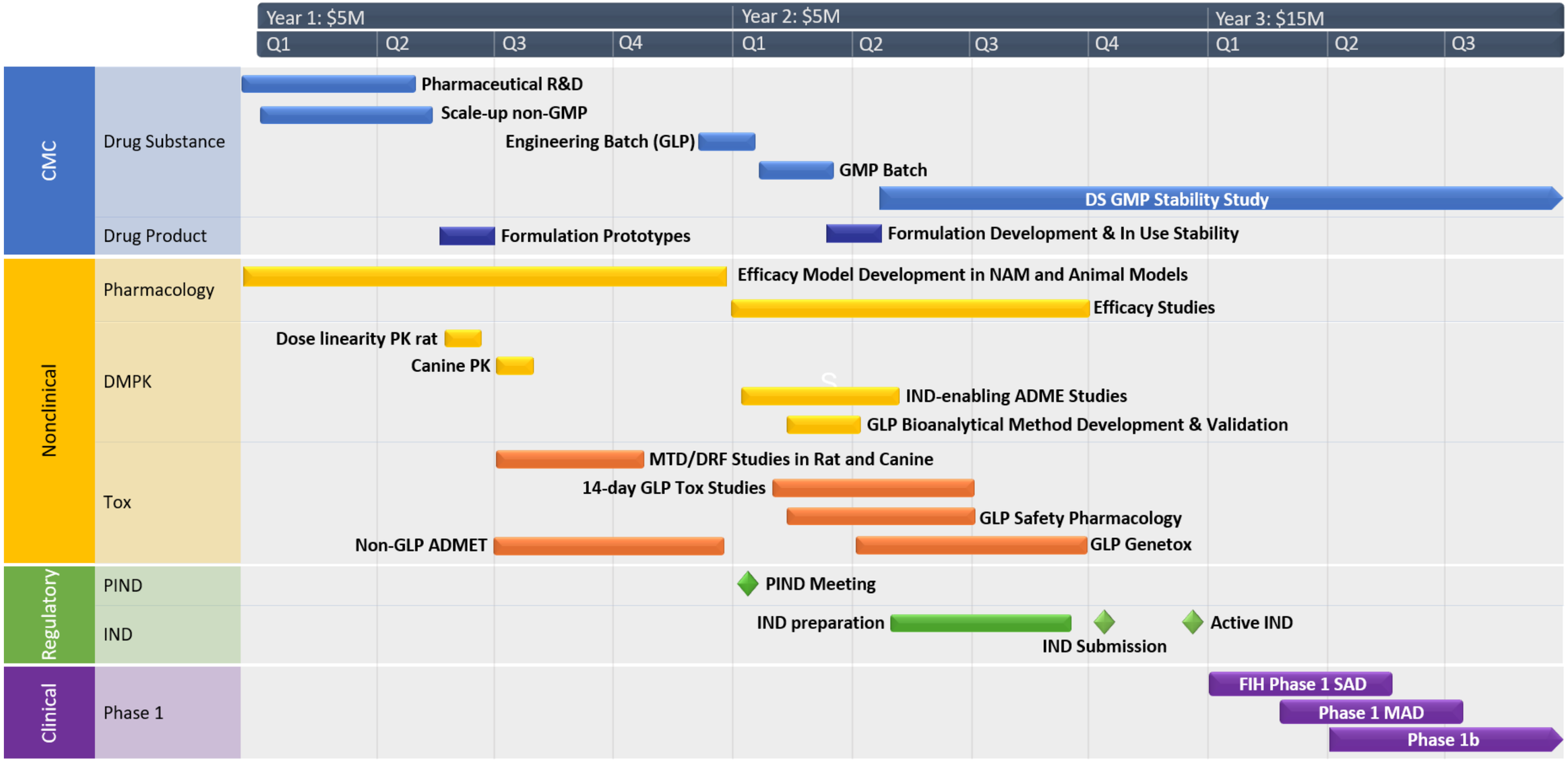
CR-0305 Development Plan to Phase 1

Timing dependent on financing and successful completion of preclinical and regulatory milestones



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Capital-Efficient Operating Model
Led by an Experienced Cardiovascular Physician-Scientist

John F. Schmedtje Jr., MD, MPH, Founder

- Northwestern University MD; Harvard School of Public Health MPH
- Former full-time faculty appointments at Baylor, UTMB, and Wake Forest
- Board-certified in Internal Medicine, Cardiovascular Disease, and Nuclear Cardiology
- 1996 Cournand & Comroe Young Investigator Prize, American Heart Association National Center
- Published research focused on hypoxia and vascular endothelium
- Four decades of collaboration in clinical trials and drug development



Operating model

- Virginia-based office and laboratory infrastructure with AI tools
- External laboratory, scientific, and legal expertise
- Planned team and governance expansion as development advances

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CR-0305: A Novel Preclinical Candidate for Refractory Angina

Significant unmet need

- 16 million Americans have CAD / 900,000 have refractory angina
- ANOCA represents a population of 3 million without an option for mechanical revascularization
- Existing pharmacologic options are limited by efficacy, tolerance, or adverse effects

Differentiated therapeutic hypothesis

- CR-0305 combines direct NO donation with a potential second mechanism involving cellular NO signaling
- The program is being developed to provide rapid vasodilation with more durable activity

Human-relevant preclinical evidence

- CR-0305 increases NO_2 and cGMP in hypoxic human coronary cell co-culture.
- CR-0305 demonstrates greater vasodilatory potency than isosorbide mononitrate in human coronary arteries *ex vivo*
- Early ADME and in vitro safety studies support continued preclinical development

Protected asset with defined development plan

- U.S. and international patent portfolio
- $1.9M secured to date from NIH SBIR, Virginia CCF, and angel investors
- Seeking $5M to advance ADME/Tox, proof-of-concept studies, API scale-up, and preparation for an FDA pre-IND meeting
- Subsequent financing would support IND-enabling work and first-in-human clinical trials

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OPENING HEARTS

Advancing a New Therapeutic Strategy For Angina with CR-0305

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