

APPLICATION FOR FEDERAL ASSISTANCE  
**SF 424 (R&R)**

|  |  | 3. DATE RECEIVED BY STATE   | State Application Identifier                                  |
|--|--|---|---|
| <b>1. TYPE OF SUBMISSION*</b>  |  | <b>4.a. Federal Identifier</b>  |   |
| <input type="radio"/> Pre-application  | <input checked="" type="radio"/> Application | <input type="radio"/> Changed/Corrected Application                           | <b>b. Agency Routing Number</b>                               |
| <b>2. DATE SUBMITTED</b>   | <b>Application Identifier</b>                | <b>c. Previous Grants.gov Tracking Number</b>                                 |   |
| <b>5. APPLICANT INFORMATION</b>  |  |   | <b>UEI*</b> : CP5VN4N2MXX3                                    |
| Legal Name*: AMALGENT THERAPEUTICS, INC.   |  |   |   |
| Department:  |  |   |   |
| Division:  |  |   |   |
| Street1*:  | 300 E First St                               |   |   |
| Street2:   |  |   |   |
| City*:   | Greenville                                   |   |   |
| County:  |  |   |   |
| State*:  | NC: North Carolina                           |   |   |
| Province:  |  |   |   |
| Country*:  | USA: UNITED STATES                           |   |   |
| ZIP / Postal Code*:  | 27858-1201                                   |   |   |
| Person to be contacted on matters involving this application   |  |   |   |
| Prefix:  | First Name*: Malcolm                         | Middle Name: A  | Last Name*: Meyn  |
| Position/Title:  | Suffix:                                      |   |   |
| Street1*:  | Chief Scientific Officer                     |   |   |
| Street2:   | 300 E First St                               |   |   |
| City*:   | Greenville                                   |   |   |
| County:  |  |   |   |
| State*:  | NC: North Carolina                           |   |   |
| Province:  |  |   |   |
| Country*:  | USA: UNITED STATES                           |   |   |
| ZIP / Postal Code*:  | 27858-1201                                   |   |   |
| Phone Number*:   | 9199231846                                   | Fax Number:   | Email: malcolm@amalgent.com                                   |
| <b>6. EMPLOYER IDENTIFICATION NUMBER (EIN) or (TIN)*</b>   |  | 84-4925461  |   |
| <b>7. TYPE OF APPLICANT*</b>   |  | R: Small Business   |   |
| Other (Specify):   |  |   |   |
| Small Business Organization Type   |  | <input type="radio"/> Women Owned   | <input type="radio"/> Socially and Economically Disadvantaged |
| <b>8. TYPE OF APPLICATION*</b>   |  | If Revision, mark appropriate box(es).  |   |
| <input checked="" type="radio"/> New   | <input type="radio"/> Resubmission           | <input type="radio"/> A. Increase Award                                       | <input type="radio"/> B. Decrease Award                       |
| <input type="radio"/> Renewal  | <input type="radio"/> Continuation           | <input type="radio"/> C. Increase Duration                                    | <input type="radio"/> D. Decrease Duration                    |
|  | <input type="radio"/> Revision               | <input type="radio"/> E. Other (specify):                                     |   |
| Is this application being submitted to other agencies?*  |  | <input type="radio"/> Yes   | <input checked="" type="radio"/> No                           |
|  |  | What other Agencies?  |   |
| <b>9. NAME OF FEDERAL AGENCY*</b><br>National Institutes of Health   |  | <b>10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER</b><br>TITLE:            |   |
| <b>11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*</b><br>Clinical Development of the First Fixed Dose Combination Pain Therapeutic with Decreased Potential for Abuse and Tolerance |  |   |   |
| <b>12. PROPOSED PROJECT</b><br>Start Date*<br>04/01/2025   |  | <b>13. CONGRESSIONAL DISTRICTS OF APPLICANT</b><br>Ending Date*<br>03/31/2027 |   |
|  |  | NC-001  |   |

**SF 424 (R&R)** APPLICATION FOR FEDERAL ASSISTANCE**14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION**

Prefix: First Name\*: MALCOLM Middle Name: A Last Name\*: MEYN Suffix:  
 Position/Title: Chief Scientific Officer  
 Organization Name\*: AMALGENT THERAPEUTICS, INC.  
 Department:  
 Division:  
 Street1\*: 300 E First St  
 Street2:  
 City\*: Greenville  
 County:  
 State\*: NC: North Carolina  
 Province:  
 Country\*: USA: UNITED STATES  
 ZIP / Postal Code\*: 27858-1201  
 Phone Number\*: 9199231846 Fax Number: Email\*: malcolm@amalgent.com

**15. ESTIMATED PROJECT FUNDING**

|                                       |                |
|---------------------------------------|----------------|
| a. Total Federal Funds Requested*     | \$3,337,736.00 |
| b. Total Non-Federal Funds*           | \$0.00         |
| c. Total Federal & Non-Federal Funds* | \$3,337,736.00 |
| d. Estimated Program Income*          | \$0.00         |

**16. IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?\***

- a. YES  THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:  
 DATE: \_\_\_\_\_
- b. NO  PROGRAM IS NOT COVERED BY E.O. 12372; OR  
 PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

**17. By signing this application, I certify (1) to the statements contained in the list of certifications\* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances \* and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)**

I agree\*

\* The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.

**18. SFLLL or OTHER EXPLANATORY DOCUMENTATION**

File Name:

**19. AUTHORIZED REPRESENTATIVE**

Prefix: First Name\*: Sam Middle Name: Last Name\*: Tetlow Suffix:  
 Position/Title\*: President, Exec Chairman  
 Organization Name\*: AMALGENT THERAPEUTICS, INC.  
 Department:  
 Division:  
 Street1\*: 300 E First St  
 Street2:  
 City\*: Greenville  
 County:  
 State\*: NC: North Carolina  
 Province:  
 Country\*: USA: UNITED STATES  
 ZIP / Postal Code\*: 27858-1201  
 Phone Number\*: 919-923-3716 Fax Number: Email\*: sam@clearviewlimited.com

**Signature of Authorized Representative\***

CHRIS Brasfield

**Date Signed\***

09/04/2024

**20. PRE-APPLICATION** File Name:**21. COVER LETTER ATTACHMENT** File Name:

## 424 R&amp;R and PHS-398 Specific

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## Project/Performance Site Location(s)

**Project/Performance Site Primary Location**

I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: AMALGENT THERAPEUTICS, INC.

UEI: CP5VN4N2MXX3

Street1\*: 300 E First St

Street2:

City\*: Greenville

County:

State\*: NC: North Carolina

Province:

Country\*: USA: UNITED STATES

Zip / Postal Code\*: 278580000

Project/Performance Site Congressional District\*: NC-001

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**Project/Performance Site Location 1**

I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: PPD

UEI:

Street1\*: 7551 Metro Center Drive

Street2:

City\*: Austin

County:

State\*: TX: Texas

Province:

Country\*: USA: UNITED STATES

Zip / Postal Code\*: 78744-1625

Project/Performance Site Congressional District\*: TX-035

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### Project/Performance Site Location 2

Organization Name: Catalent Greenville, Inc  
UEI:  
Street1\*: P.O. Box 734097  
Street2:  
City\*: Chicago  
County:  
State\*: IL: Illinois  
Province:  
Country\*: USA: UNITED STATES  
Zip / Postal Code\*: 60673-4097  
Project/Performance Site Congressional District\*: IL-007

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#### Additional Location(s)

File Name:

I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

**RESEARCH & RELATED Other Project Information**

|  |  |
|--|--|
| <b>1. Are Human Subjects Involved?*</b> <input checked="" type="radio"/> Yes <input type="radio"/> No  |  |
| 1.a. If YES to Human Subjects  |  |
| Is the Project Exempt from Federal regulations? <input type="radio"/> Yes <input checked="" type="radio"/> No  |  |
| If YES, check appropriate exemption number: <input type="radio"/> 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4 <input type="radio"/> 5 <input type="radio"/> 6 <input type="radio"/> 7 <input type="radio"/> 8                |  |
| If NO, is the IRB review Pending? <input checked="" type="radio"/> Yes <input type="radio"/> No  |  |
| IRB Approval Date:   |  |
| Human Subject Assurance Number none  |  |
| <b>2. Are Vertebrate Animals Used?*</b> <input type="radio"/> Yes <input checked="" type="radio"/> No  |  |
| 2.a. If YES to Vertebrate Animals  |  |
| Is the IACUC review Pending? <input type="radio"/> Yes <input type="radio"/> No  |  |
| IACUC Approval Date:   |  |
| Animal Welfare Assurance Number  |  |
| <b>3. Is proprietary/privileged information included in the application?*</b> <input checked="" type="radio"/> Yes <input type="radio"/> No  |  |
| <b>4.a. Does this project have an actual or potential impact - positive or negative - on the environment?*</b> <input type="radio"/> Yes <input checked="" type="radio"/> No   |  |
| 4.b. If yes, please explain:   |  |
| 4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an <input type="radio"/> Yes <input type="radio"/> No environmental assessment (EA) or environmental impact statement (EIS) been performed? |  |
| 4.d. If yes, please explain:   |  |
| <b>5. Is the research performance site designated, or eligible to be designated, as a historic place?*</b> <input type="radio"/> Yes <input checked="" type="radio"/> No   |  |
| 5.a. If yes, please explain:   |  |
| <b>6. Does this project involve activities outside the United States or partnership with international collaborators?*</b> <input type="radio"/> Yes <input checked="" type="radio"/> No   |  |
| 6.a. If yes, identify countries:   |  |
| 6.b. Optional Explanation:   |  |
| 7. Project Summary/Abstract* Filename PSummary_AT_FT_2024.08.30.pdf  |  |
| 8. Project Narrative* PNarrative_AT_FT_2024.08.30.pdf  |  |
| 9. Bibliography & References Cited Lit_cited_merged_AT_FT_2024.08.30.pdf   |  |
| 10. Facilities & Other Resources Facilities_AT_FT_2024.09.02.pdf   |  |
| 11. Equipment Equip_AT_FT_2024.09.02.pdf   |  |

**PROJECT SUMMARY:** Amalgent Therapeutics is developing an innovative solution to address critical issues associated with opioid use in pain management, such as opioid use disorder (OUD) and opioid tolerance. The opioid crisis resulted in an estimated 80,000 deaths in the United States in 2023 alone. Despite significant risks, there have been no new FDA-approved non-opioid drugs for severe pain in 10 years, leaving a gap in safe and effective pain treatments. To address this gap, Amalgent is leveraging crosstalk between dopamine and opioid signaling pathways to enhance pain relief while mitigating the risks of addiction and tolerance associated with traditional opioid therapies. To this end, they have repurposed pramipexole, an FDA-approved drug initially used for Parkinson's disease, into a safe, effective low-dose morphine pain medication called AMGT-0220. Preclinical data shows that pramipexole enhances morphine's pain-relieving effects while reducing opioid-seeking behavior and tolerance. The combination of these two FDA-approved drugs not only promises significant clinical benefits but also expedites the regulatory approval process using the 505(b)2 pathway, confirmed during a Pre-IND meeting. The commercial potential for AMGT-0220 is robust, as it addresses an urgent need for safer pain medications within a multi-billion dollar market. Based on FDA feedback, Amalgent is positioned to prepare an IND submission package to carry out the first-in-human study. In this SBIR Fast-Track project, Amalgent will 1) manufacture clinical batches of AMGT-0220; 2) prepare and submit an IND application by compiling existing preclinical toxicology, safety pharmacology, and CMC data, preparing and finalizing reports, and preparing clinical protocols; 3) conduct a Phase 1 pharmacokinetic study in healthy volunteers to analyze the safety and efficacy of AMGT-0220. Successful commercialization of AMGT-0220 will make significant advances in pain management, offering new hope for patients and potentially changing the landscape of opioid therapy.

**PROJECT NARRATIVE:** Amalgent Therapeutics is addressing the critical need of effective medications for moderate to severe pain that reduce the risks of addiction, tolerance, and overdose associated with current opioid medications. Their drug candidate AMGT-0220 is a novel pain medication that combines an FDA-approved Parkinson's drug with a subtherapeutic dose of morphine to offer effective pain relief while minimizing dependency risks. This medication will enhance patient safety, providing a much-needed alternative to current high-risk opioid therapies.

## FACILITIES AND OTHER RESOURCES

**Environment** – Amalgent Therapeutics is based in the offices of the Innovation Center in the Willis Building at East Carolina University in Greenville, NC. In addition, the company has access to the facilities at the North Carolina Biotechnology Center in Research Triangle Park, North Carolina. The center offers shared workspaces and fully furnished offices, US mailing address, UPS and Fedex delivery services, private VOIP phones with phone numbers for each office and workspace, high-speed internet, reception services, building-adjacent free parking, kitchen space, and two conference rooms. This Center provides access and introductions to all departments, including Emerging Company Development, Economic Development, Grants and Loans, Ag Tech, Science & Tech Development, Business & Development, Life Science Intelligence. They will help in obtaining leads on long-term office and lab space and invitations to industry professional and social events that draw 60,000 attendees annually.

**Willis Building, Greenville, NC**



**North Carolina Biotechnology Center,  
Research Triangle Park ,NC**



**North Carolina Biotechnology Center, Office Space**



**Office** Amalgent leases an office of approximately 100 sq ft with access to meeting rooms and computer services. Through the Biotechnology Center, they have free use of two conference rooms and library access.

**Computer** – The main office and staff home offices are equipped with a laptop and/or desktop, printer, and phone. The computers have all needed software to carry out their work, including Microsoft office. All staff have password-protected access to secure, dedicated DropBox.

**Intellectual Property** – Amalgent has a worldwide exclusive license to inventions made by Kori Brewer, Ph.D., and Stefan Clemens, PhD. of East Carolina University. The corresponding patent, "Methods and Composition for Maintaining Opioid Efficacy in the Treatment of Chronic Pain," was issued on December 21, 2021, as Patent No. 11,202,777. Claims are directed towards the treatment of pain in a subject, comprising administering an effective amount of an opioid and a dopamine type 3 receptor agonist, where the said combination can also reduce or inhibit opioid tolerance, addiction, and dependence. Patents are actively being pursued in Canada and Europe.

**Laboratory** – All non-clinical laboratory work for the proposed project will be performed by our selected CDMO Catalent Pharma Solutions, LLC. The facilities details for Catalent are described in "Other" below.

**Biohazards Handling and Disposal** – Any work with biohazards performed by our clinical research organization (PPD) will be performed in a BSL-2 laboratory containing a Class II Biological Safety cabinet to protect against exposure to aerosols. Laboratory personnel will wear appropriate personal protective equipment, including lab coats, gloves, and, if necessary, safety glasses. All consumables (plastic tubes, syringes, serological pipettes, pipette tips) and debris will be discarded as biohazard waste.

**Clinical** – The clinical study being performed in this Fast Track project and the associated bioanalytical analysis of samples will be performed by PPD. Please see description under "Other".

**Animal** – No work will be performed with animals in this project.

**Other** – CDMO/CRO Facilities

### **1. Catalent Pharma Solutions, LLC**

Catalent is a leading CDMO with over 75 years of experience with extensive expertise development sciences, delivery technologies, and multi-modality manufacturing. They have over 1000 products in development at any time and have extensive partnerships with pharmaceutical and biopharmaceutical companies. Its Greenville, NC location, located at 1240 Sugg Parkway, consists of a state-of-the-art 333,000 sq. ft. facility that specializes in end-to-end turn-key solutions for oral solid dosage forms. Its services include integrated formulation development, analytical services, commercial manufacturing, and packaging. The facility is FDA accredited .

### **2. Austin Clinical Research Unit - PPD Phase 1 Clinic**

PPD is a clinical research business of Thermo Fisher Scientific, who has conducted clinical trials in more than 100 countries as a means of deliver life-changing therapies to improve health. They provide drug development, laboratory, and lifecycle services to customers across pharmaceutical, biotechnology, medical device, academic and government entities. Our Phase I study to evaluate the safety, pharmacokinetics, and relative bioavailability of our drug candidate will be performed at PPD's Austin Clinical Research Unit (CRU) located at 7551 Metro Center Drive, Austin, TX, is one of the largest clinics serving early and late phase study needs. The 152,000-square-foot facility has 200 beds for both early and late phase clinical pharmacology studies, specifically designed to accommodate either short-term or long-term stays. The facility also has a dedicated outpatient facility. They have an established Human Safety Committee (HSC) that oversees all study stages to ensure the appropriate safety, medical and scientific oversight. Studies performed at this CRU include first-in-human, single ascending dose/multiple ascending dose, pharmacokinetics/pharmacodynamics, bioavailability/bioequivalence, drug-drug interaction, food effect, thorough QT, human absorption, metabolism and excretion, and age and gender-specific studies. Additional features of the CRU facility include a centralized procedure suite for closer monitoring in hospital-like individual subject rooms, cardiac monitoring with telemetry capacity of 32 channels., a 3,000-sq. ft. pharmacy that adheres to United States Pharmacopeia (USP) 797, 795 and 800 guidelines for aseptic drug preparation, streamlined PK processing laboratory with centralized work areas and an expanded Phase I-III Clinical Laboratory Improvement Amendments (CLIA) and College of American Pathologists (CAP) accredited central laboratory capable of performing a wide clinical menu of tests seven days a week, on-site kitchen for all study dietary needs, and ACLS-certified paramedics on site 24 hours a day for safety monitoring, under the guidance of the medical director. The bioanalytical analysis of the pharmacokinetic samples will be performed at PPD's GMP lab at 8551 Research Way, Suite 90 Middleton, WI.

## EQUIPMENT

### **Amalgent Therapeutics, Inc.**

Amalgent Therapeutics uses a Dell desktop (Intel i7-7700, 16.0 GB RAM, Samsung 28" display) and multiple Lenovo Yoga laptop computers. Software includes full Microsoft Office and Smartsheet subscriptions. DropBox is used for the storage and sharing of company documents.

### **Catalent Pharma Solutions, LLC**

#### Physical Properties & Solid State

**X-Ray Powder Diffraction:** Bruker AXS D8 Discover; Panalytical Xpert Pro MPD

**HPLC:** Agilent 1100, 1200, 1260, 1290; Waters H-class and 2695Detector Types: UV/PDA/ELSD/CAD/FL/RI/DAD/VWD/VMD

**FTIR / TGA-IR / DSC:** ThermoNicolet 6700; TA Instruments Q5000; TA Instruments Q200 and Q2000

**Dynamic Vapor Sorption:** SMS DVC Advantage

**FT-Raman Spectrometer:** ThermoNicolet NXR 9650

**Centrifuge Evaporator (vacuum):** Genevac EZ-2

**Microscope with Digital Camera:** Olympus BX51 / Olympus; BX60 / Olympus SZX12

**Powder Dispensing Robot:** Autodose/Unchained Labs; PowderiumVarian Varian Tablet

**Capillary Melting Point Apparatus with Video:** SRS Optimelt

**Lyophilizers (up to ~10g):** Virtis Ly-Centre/Virtis Advantage Plus

#### Organic Spectroscopy

**Impurity Identification & Characterization:** Mass Spectrometry: Waters; Xevo QToF / LTQ XL

**Reference Material Characterization:** NMR: 500 MHz NMR System; Spectroscopy: FTIR, TGA, DSC, UV-Vis; Mass Spectrometry: Waters Xevo QToF / LTQ XL / Sciex 5000 Triple Quadrupole

**Nitrosamines: MD/MV, Screening:** AB Sciex 5000

#### Microbiology

**Sterility Testing:** Getinge Isolator ISL-03; JUMO Pressure Transmitter on ISL-03

**Endotoxin Testing:** Siemens Desigo BMS Panel 11

**Total Organic Carbon (TOC) Analyzer:** GE/SUEZ TOC Analyzer

**Autoclave:** Tuttnauer 3850 EL

**Plate Reader:** Biotek ELX808IUCR

**Microscopes:** Lieder ME-643

#### Analytical Development (Method Transfer/Development/ Validation) & Stability

**HPLC:** Agilent 1200, 1260, 1290; Waters H-class and 2695; 2 D HPLC (Agilent 1100 and 1290) Detector Types: UV/PDA/ ELSD/CAD/FL/RI

**Gas Chromatography FID & TCD:** Agilent 6890N with Agilent 7683 Series Injector; Agilent 6890N with Agilent 7684 Headspace Oven

**Ion Chromatography:** DionexTM IC-5000, IC-3000

**Dissolution:** USP Apparatus 1, 2, 3, and 4; Agilent 708 Distek 2100A; Hanson Vision® Elite 8TM; Sotax CE 7smart flow-through tester; Varian Bio-Dis; Agilent Sampling Stations: VK8000 and 850DS

**KF:** Coulometric (with/without oven) - Brinkmann 756 Coulometer (Metrohm), Volumetric - Brinkmann 758 KFD Titrino (Metrohm)

**Particle Sizing:** Malvern Mastersizer 3000 / Mastersizer 3000 Aero S / Mastersizer 3000 Hydro MV / Mastersizer 3000 Hydro SV

MiniCapt 100187

**Particle Counting:** Beckman Coulter HIAC Liquid Particle Counter

**Radiation Testing:** Agilent 1200 HPLC with GABI NOVA gamma detector

#### Stability Testing & Storage

**HPLC:** Agilent 1100, 1200, 1600 Detector types: UV/PDA/ ELSD/CAD/FL/RI

**Ion Chromatography:** DionexTM IC-5000, IC-5000+

**Dissolution:** USP Apparatus 1, 2, 3, and 4, Agilent 708, Distek 2100A, Hanson Vision® Elite 8TM, Sotax CE, 7Smart Flow-Through Tester Varian Bio-Dis, Agilent Sampling Stations (VK8000 and 850DS)

**FTIR:** Thermo Vicolet iS50

**Automatic Titrations:** Mettler Toledo T5 Excellence

**UV-VIS:** Agilent G1103B

**Particle Size Distribution:** Malvern Mastersizer 3000

Elemental Impurities/Inorganics

**ICP-MS:** Agilent 7700 and 7900 series

**FAAS:** PinAAcle 900T Flame AA Perkin Elmer

**PPD**

Bioanalytical analysis of study samples will be performed at PPD's GMP lab in Middleton, Wisconsin. The available equipment include:

Method Development and Validation/Process Cleaning Validation

**Chromatography:** HPLC, UPLC, TOC, GC, SEC and IC with the following detection capabilities: UV, DAD, FL, MS, ELSD, RI, PAD, FID, TCD, MALS, CAD

**Dissolution:** IR, ER, MR

**RESEARCH & RELATED Senior/Key Person Profile (Expanded)**

| PROFILE - Project Director/Principal Investigator |                             |         |                              |             |      |         |
|---|-----------------------------|---------|------------------------------|-------------|------|---------|
| Prefix:   | First Name*:                | MALCOLM | Middle Name A                | Last Name*: | MEYN | Suffix: |
| Position/Title*:                                  | Chief Scientific Officer    |         |                              |             |      |         |
| Organization Name*:                               | AMALGENT THERAPEUTICS, INC. |         |                              |             |      |         |
| Department:                                       |                             |         |                              |             |      |         |
| Division:   |                             |         |                              |             |      |         |
| Street1*:   | 300 E First St              |         |                              |             |      |         |
| Street2:  |                             |         |                              |             |      |         |
| City*:  | Greenville                  |         |                              |             |      |         |
| County:   |                             |         |                              |             |      |         |
| State*:   | NC: North Carolina          |         |                              |             |      |         |
| Province:   |                             |         |                              |             |      |         |
| Country*:   | USA: UNITED STATES          |         |                              |             |      |         |
| Zip / Postal Code*:                               | 27858-1201                  |         |                              |             |      |         |
| Phone Number*:                                    | 9199231846                  |         | Fax Number:                  |             |      |         |
| E-Mail*:  | malcolm@amalgent.com        |         |                              |             |      |         |
| Credential, e.g., agency login: mameyn            |                             |         |                              |             |      |         |
| Project Role*:                                    | PD/PI                       |         | Other Project Role Category: |             |      |         |
| Degree Type:                                      | PHD,BA                      |         | Degree Year: 1997,1989       |             |      |         |
| Attach Biographical Sketch*:                      | File Name:                  |         | 1_Bio_Meyn_2024.09.02.pdf    |             |      |         |
| Attach Current & Pending Support:                 | File Name:                  |         |                              |             |      |         |

| PROFILE - Senior/Key Person              |                             |                |                              |         |
|--|-----------------------------|----------------|------------------------------|---------|
| Prefix:                                  | First Name*: Sam            | Middle Name C. | Last Name*: Tetlow           | Suffix: |
| Position/Title*:                         | President, Exec Chairman    |                |                              |         |
| Organization Name*:                      | AMALGENT THERAPEUTICS, INC. |                |                              |         |
| Department:                              |                             |                |                              |         |
| Division:                                |                             |                |                              |         |
| Street1*:                                | 300 E First St              |                |                              |         |
| Street2:                                 |                             |                |                              |         |
| City*:                                   | Greenville                  |                |                              |         |
| County:                                  |                             |                |                              |         |
| State*:                                  | NC: North Carolina          |                |                              |         |
| Province:                                |                             |                |                              |         |
| Country*:                                | USA: UNITED STATES          |                |                              |         |
| Zip / Postal Code*:                      | 27858-1201                  |                |                              |         |
| Phone Number*:                           | 919-923-3716                |                | Fax Number:                  |         |
| E-Mail*:                                 | sam@clearviewlimited.com    |                |                              |         |
| Credential, e.g., agency login: S.TETLOW |                             |                |                              |         |
| Project Role*:                           | Co-Investigator             |                | Other Project Role Category: |         |
| Degree Type:                             | MBA, BS                     |                | Degree Year: 2003, 1993      |         |
| Attach Biographical Sketch*:             | File Name:                  |                | 2_Bio_Tetlow_2024.08.24.pdf  |         |
| Attach Current & Pending Support:        | File Name:                  |                |                              |         |

| PROFILE - Senior/Key Person             |                            |             |  |         |
|---|----------------------------|-------------|--|---------|
| Prefix:                                 | First Name*: Brian         | Middle Name | Last Name*: Spears                                   | Suffix: |
| Position/Title*:                        | Associate Medical Director |             |  |         |
| Organization Name*:                     | PPD                        |             |  |         |
| Department:                             | Clinical Research Unit     |             |  |         |
| Division:                               |                            |             |  |         |
| Street1*:                               | 7551 Metro Center Drive    |             |  |         |
| Street2:                                |                            |             |  |         |
| City*:                                  | Austin                     |             |  |         |
| County:                                 |                            |             |  |         |
| State*:                                 | TX: Texas                  |             |  |         |
| Province:                               |                            |             |  |         |
| Country*:                               | USA: UNITED STATES         |             |  |         |
| Zip / Postal Code*:                     | 78744-1625                 |             |  |         |
| Phone Number*:                          | 000-000-0000               |             | Fax Number:  |         |
| E-Mail*:                                | brian.spears@ppd.com       |             |  |         |
| Credential, e.g., agency login: SPEARSB |                            |             |  |         |
| Project Role*:                          | Other (Specify)            |             | Other Project Role Category: Clinical Site Clinician |         |
| Degree Type:                            | MD, BS                     |             | Degree Year: 2010, 2006                              |         |
| Attach Biographical Sketch*:            | File Name:                 |             | 3_Bio_Spears_2024.08.30.pdf                          |         |
| Attach Current & Pending Support:       | File Name:                 |             |  |         |

| PROFILE - Senior/Key Person              |                         |         |  |             |        |         |
|--|-------------------------|---------|--|-------------|--------|---------|
| Prefix:                                  | First Name*:            | Charles | Middle Name E.   | Last Name*: | Argoff | Suffix: |
| Position/Title*:                         | Professor of Neurology  |         |  |             |        |         |
| Organization Name*:                      | Albany Medical College  |         |  |             |        |         |
| Department:                              |                         |         |  |             |        |         |
| Division:                                |                         |         |  |             |        |         |
| Street1*:                                | 47 New Scotland Avenue  |         |  |             |        |         |
| Street2:                                 | Department of Neurology |         |  |             |        |         |
| City*:                                   | Albany                  |         |  |             |        |         |
| County:                                  |                         |         |  |             |        |         |
| State*:                                  | NY: New York            |         |  |             |        |         |
| Province:                                |                         |         |  |             |        |         |
| Country*:                                | USA: UNITED STATES      |         |  |             |        |         |
| Zip / Postal Code*:                      | 122080000               |         |  |             |        |         |
| Phone Number*:                           | 518-262-5226            |         | Fax Number:  |             |        |         |
| E-Mail*:                                 | argoffc@mail.amc.edu    |         |  |             |        |         |
| Credential, e.g., agency login: ARGOFFCE |                         |         |  |             |        |         |
| Project Role*:                           | Other (Specify)         |         | Other Project Role Category: Other Significant Contributor |             |        |         |
| Degree Type:                             | MD,BMS                  |         | Degree Year: 1984,1982                                     |             |        |         |
| Attach Biographical Sketch*:             | File Name:              |         | 4_Bio_Argoff_2024.09.03.pdf                                |             |        |         |
| Attach Current & Pending Support:        | File Name:              |         |  |             |        |         |

| PROFILE - Senior/Key Person                |                      |        |  |             |       |         |
|--|----------------------|--------|--|-------------|-------|---------|
| Prefix:                                    | First Name*:         | Gerald | Middle Name L  | Last Name*: | Klein | Suffix: |
| Position/Title*:                           | Principal            |        |  |             |       |         |
| Organization Name*:                        | MedSurgPI            |        |  |             |       |         |
| Department:                                |                      |        |  |             |       |         |
| Division:                                  |                      |        |  |             |       |         |
| Street1*:                                  | 3700 Lark Farm Rd    |        |  |             |       |         |
| Street2:                                   |                      |        |  |             |       |         |
| City*:                                     | Franklinton          |        |  |             |       |         |
| County:                                    |                      |        |  |             |       |         |
| State*:                                    | NC: North Carolina   |        |  |             |       |         |
| Province:                                  |                      |        |  |             |       |         |
| Country*:                                  | USA: UNITED STATES   |        |  |             |       |         |
| Zip / Postal Code*:                        | 275250000            |        |  |             |       |         |
| Phone Number*:                             | 000-000-0000         |        | Fax Number:  |             |       |         |
| E-Mail*:                                   | gklein@medsurgpi.com |        |  |             |       |         |
| Credential, e.g., agency login: GERRYKLEIN |                      |        |  |             |       |         |
| Project Role*:                             | Other (Specify)      |        | Other Project Role Category: Other Significant Contributor |             |       |         |
| Degree Type:                               | MD, BS               |        | Degree Year: 1975, 1969                                    |             |       |         |
| Attach Biographical Sketch*:               | File Name:           |        | 5_Bio_Klein_2024.08.30.pdf                                 |             |       |         |
| Attach Current & Pending Support:          | File Name:           |        |  |             |       |         |

| PROFILE - Senior/Key Person               |                             |               |  |         |
|---|-----------------------------|---------------|--|---------|
| Prefix:                                   | First Name*: Timothy        | Middle Name R | Last Name*: Wright   | Suffix: |
| Position/Title*:                          | Strategic Advisor           |               |  |         |
| Organization Name*:                       | AMALGENT THERAPEUTICS, INC. |               |  |         |
| Department:                               |                             |               |  |         |
| Division:                                 |                             |               |  |         |
| Street1*:                                 | 300 E First St              |               |  |         |
| Street2:                                  |                             |               |  |         |
| City*:                                    | Greenville                  |               |  |         |
| County:                                   |                             |               |  |         |
| State*:                                   | NC: North Carolina          |               |  |         |
| Province:                                 |                             |               |  |         |
| Country*:                                 | USA: UNITED STATES          |               |  |         |
| Zip / Postal Code*:                       | 27858-1201                  |               |  |         |
| Phone Number*:                            | 617-678-7607                |               | Fax Number:  |         |
| E-Mail*:                                  | wrightt58@aol.com           |               |  |         |
| Credential, e.g., agency login: TIMWRIGHT |                             |               |  |         |
| Project Role*:                            | Other (Specify)             |               | Other Project Role Category: Other Significant Contributor |         |
| Degree Type:                              | BSc                         |               | Degree Year: 1981  |         |
| Attach Biographical Sketch*:              | File Name:                  |               | 6_Bio_Wright_2024.09.04.pdf                                |         |
| Attach Current & Pending Support:         | File Name:                  |               |  |         |

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors.  
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Malcolm A Meyn, III

eRA COMMONS USER NAME (credential, e.g., agency login): mameyn

POSITION TITLE: Chief Scientific Officer

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.*)

| INSTITUTION AND LOCATION                      | DEGREE<br>(if applicable) | Completion Date<br>MM/YYYY | FIELD OF STUDY                   |
|---|---------------------------|----------------------------|----------------------------------|
| Macalester College, St. Paul, MN              | BA                        | 05/1989                    | Biology/Political Science        |
| University of Minnesota, Minneapolis, MN      |                           | 05/1991                    | Chemistry/Mathematics            |
| University of Arizona, Tucson, AZ             | PhD                       | 12/1997                    | Microbial Genetics               |
| Howard Hughes Medical Institute, Philadelphia | Postdoctoral              | 05/2002                    | Signaling Biology                |
| University of Pittsburgh, Pittsburgh, PA      | Postdoctoral              | 05/2006                    | Signaling Biology                |
| University of Washington                      |                           | 09/2014                    | Biotechnology Project Management |
| George Washington University, Washington, DC  | MSHS                      | 05/2020                    | Regulatory Affairs               |

**A. Personal Statement**

I am a trained biochemistry and cell biology researcher with experience in the development of new technologies for clinical studies. I have over 20 years of experience in basic research, applied research, and drug development. As an academic scientist, I focused on fundamental biologic problems related to cell signaling and the biochemical response of cells to therapeutics and naturally occurring paracrine signals. Since entering the biotechnology industry in 2011, I have focused on advancing therapeutic candidates from the research stage to Phase 1 and Phase 2 clinical trials. This experience includes generating and executing plans for R&D programs, IND-enabling studies, and human clinical development. This work incorporated the design and management of biotechnology projects in regulated and unregulated environments, managing and auditing CROs and vendors, and acting as the nonclinical lead in multidisciplinary teams in the preparation of pre-IND and IND documents and in meetings with the FDA. In addition to my Ph.D., I earned a master's degree that furthered my knowledge of the regulatory aspects of drug development, clinical trial design, and leadership in the biomedical industry. This combination of experience and academic training puts me in an excellent position to lead the development of the proposed fixed-dose combination product. I am familiar with the signaling biochemistry underlying the biology of the proposed pramipexole adjuvant and have experience moving an asset at this stage of development to clinical trials. Especially crucial for developing a therapeutic of this level of technology is my experience working with clinical, regulatory, and pharmacology experts to design, implement, and execute drug development programs. I have applied this experience to my work at Amalgent Therapeutics by starting and managing the development of our first asset, AMGT-0220, a combination of pramipexole with morphine. This includes licensing the asset, participating in a \$1M private raise, leading the effort as PI for an awarded Phase 2 SBIR, managing the pre-IND meeting process, and managing the CMC development through prototype manufacturing. I am also PI on a recently awarded Phase I SBIR for work on our next combination pain medication. This experience and expertise position me to lead the program described in this Fast Track proposal focused on the preparation of the AMGT-0220 clinical batch, IND submission, and the Phase I open-label clinical trial in healthy volunteers.

Ongoing Research Support

**1R43DA059522-01**

Meyn, Malcolm, Role: PI

08/01/2024–02/28/2025

Mechanism and Efficacy of a Novel Opioid Adjuvant

**1R44DA059302-01**

Meyn, Malcolm

09/01/2023–08/31/2025

Development of an Opioid Sparing Therapeutic to Minimize Opioid Use Disorder and Tolerance in the Treatment of Pain

**B. Positions, Scientific Appointments, and Honors**

**Positions and Employment**

|            |  |
|------------|--|
| 2020-      | Chief Scientific Officer, Amalgent Therapeutics Inc, Greenville, NC  |
| 2015-      | Chief Biotechnology Consultant, ZForm Consulting, Chapel Hill, NC  |
| 2011-2015  | Director, Pre-Clinical Development, Stemnion, Inc. (now Noveome), Pittsburgh, PA   |
| 2011-2015  | Principal Scientist, Research and Development, Stemnion, Inc. (now Noveome), Pittsburgh, PA                              |
| 2006-2011  | Research Assistant Professor, Department of Microbiology and Molecular Genetics, University of Pittsburgh Medical School |
| 2002-2006  | Research Associate, Department of Molecular Genetics and Biochemistry, University of Pittsburgh Medical School           |
| 1997- 2002 | Postdoctoral Fellow, Howard Hughes Medical Institute, University of Pennsylvania Medical School                          |
| 1992-1997  | Graduate Associate, Department of Plant Pathology, University of Arizona   |

**Other Experience and Professional Memberships**

|                |  |
|----------------|--|
| 2020 – present | Member, Regulatory Affairs Professionals Society                           |
| 2008-2015      | Member, International Society for Stem Cell Research                       |
| 1993-1997      | Member, American Society of Phytopathology                                 |
| 1995           | Graduate Instructor, Department of Microbiology, University of Arizona     |
| 1992           | Graduate Instructor, Department of Microbiology, University of Arizona     |
| 1988-1989      | Teaching Assistant, Department of Biology, Macalester College, Spring 1989 |

**C. Contributions to Science**

1. As Chief Scientific Officer of Amalgent Therapeutics, Inc., I led early-stage development efforts for the development of AMGT-0220, a novel combination product for the treatment of pain, and other combination pain products.

- a. Collaborated with co-founder to raise a \$850,000 seed round from private investors and to secure a \$250,000 low interest loan from the North Carolina Biotechnology Center.
- b. Managed Amalgent's pre-IND efforts, culminating in a successful pre-IND meeting in December 2021.
- c. Finalist in regional biotechnology competition.
- d. Secured SBIR funding to support projects (see Personal Statement)

2. I discovered the role of cyclins and cyclin degradation in maintaining stable metaphase cell cycle arrest following DNA damage. A critical DNA damage checkpoint in *Saccharomyces cerevisiae* is the arrest of the cell cycle at the metaphase stage of mitosis. In early postdoctoral work at the University of Pennsylvania, I demonstrated that yeast strains mutated for two cyclins, Clb5 and Clb6, were hypersensitive to DNA damage, bypassed the metaphase checkpoint, and arrested instead with separated sister chromatids. Furthermore, unlike wild-type cells, clb5 clb6 mutants undergo nuclear division despite the presence of nuclear non-degradable Pds1. These results suggested a novel role for the S-phase cyclins in maintaining sister chromatid cohesion during a metaphase arrest.

- a. **Meyn, M. A.**, and Holloway, S.L. (2000). S-phase cyclins are required for a stable arrest at metaphase. *Curr. Biol.* 10, 1599–1602.
- b. Hendrickson, C., **Meyn, M. A.**, Morabito, L., and Holloway, S.L. (2001). The KEN box regulates Clb2 proteolysis in G1 and at the metaphase-to-anaphase transition. *Curr. Biol.* 11, 1781–1787.
- c. **Meyn, M. A.**, Melloy, P.G., Li, J., and Holloway, S.L. (2002). The destruction box of the cyclin Clb2 binds the anaphase-promoting complex/cyclosome subunit Cdc23. *Arch. Biochem. Biophys.* 407, 189–195.
3. I demonstrated that members of the Src Family of Tyrosine Kinases directly phosphorylate and regulate the transforming activity of oncogenic protein Bcr-Abl. Bcr-Abl is the oncogenic protein-tyrosine kinase responsible for chronic myelogenous leukemia. During my postdoctoral fellowship at the University of Pittsburgh in the laboratory of Dr. Thomas Smitgall, I demonstrated the Src family kinase members Hck, Lyn, and Fyn strongly phosphorylated the SH3-SH2 region of Bcr-Abl at seven tyrosine residues. In particular, SH3 domain Tyr89 was strongly phosphorylated in chronic myelogenous leukemia cells in a Src family kinase-dependent manner. Further work showed that mutation of this residue substantially reduced Bcr-Abl-mediated transformation of TF-1 myeloid cells to cytokine independence. The positions of these tyrosines in the crystal structure of the c-Abl core and the transformation defect of the corresponding Bcr-Abl mutants together suggest that phosphorylation of the SH3-SH2 region by Src family kinases impacts Bcr-Abl protein conformation and signaling.
- a. **Meyn, M. A.**, Wilson, M.B., Abdi, F. a, Fahey, N., Schiavone, A.P., Wu, J., Hochrein, J.M., Engen, J.R., and Smithgall, T.E. (2006). Src family kinases phosphorylate the Bcr-Abl SH3-SH2 region and modulate Bcr-Abl transforming activity. *J. Biol. Chem.* 281, 30907–30916.
4. I discovered that members of the highly homologous Src family of tyrosine kinases can act in opposition to each other during the differentiation of embryonic stem cells. At least eight of the Src family of kinases (SFKs) are present in murine embryonic stem (mES) cells. It has been argued that the members of this tyrosine kinase family have redundant functions. However, complete chemical inhibition of SFK activity blocks mES cell differentiation, yet sole inhibition of the SFK member c-Yes induces differentiation. To understand this dichotomy, as a faculty member at the University of Pittsburgh, my lab generated SFK mutants with engineered resistance to a global SFK inhibitor. We demonstrated that the presence of an inhibitor-resistant c-Src mutant, but not analogous mutants of the SFKs Hck, Lck, c-Yes, or Fyn, reversed the differentiation block associated with inhibitor treatment. These results showed that distinct SFK signaling pathways regulate mES cell fate and that the activity of some SFKs negatively regulate the activity of others. This work has led to new thinking in how the SFK works as a regulatory network in development and the onset of cancer.
- a. **Meyn, M.A.**, Schreiner, S.J., Dumitrescu, T.P., Nau, G.J., and Smithgall, T.E. (2005). SRC family kinase activity is required for murine embryonic stem cell growth and differentiation. *Mol. Pharmacol.* 68, 1320–1330.
- b. **Meyn, M. A.**, and Smithgall, T.E. (2009). Chemical genetics identifies c-Src as an activator of primitive ectoderm formation in murine embryonic stem cells. *Sci. Signal.* 2, ra64. PMC2775445
- c. Zhang, X., **Meyn, M.A.**, and Smithgall, T.E. (2014). c-Yes tyrosine kinase is a potent suppressor of ES cell differentiation and antagonizes the actions of its closest phylogenetic relative, c-Src. *ACS Chem. Biol.* 9, 139–146. PMC3875617
5. I developed novel biotherapeutics for the treatment of wound healing indications. Wound healing is a complex biologic event that requires a large number of molecules to be active at a precise location in exact concentrations. While at Stemnion, I participated in the development and initial clinical trials of ST266, a first-of-its-kind, multi-targeted, non-cellular platform biologic with the potential to improve patients' outcomes across a range of challenging wound healing diseases and conditions. ST266 is produced by collecting the secretome from a novel population of cells generated by a proprietary method of culturing amnion-derived epithelial cells from donated full-term placentas, normally discarded after birth. My responsibilities included the development of new formulations, improvements in manufacturing strategy, the development of novel activity assays, Phase 1 clinical trial design, and representing the pre-clinical team in multiple pre-IND and IND submissions and accompanying FDA meetings. ST266 is currently in multiple clinical trials.
- a. Grammer, V, **Meyn, M.A.**, and Rupp, R.G. Novel Cell Compositions and Methods. Publication number 20150196603, filed August 2, 2013, Publication Date July 16, 2015
- b. **Meyn, M.A.**, Fried, C.A. Olejniczak, D.M. and Rupp, R.G. Cell-derived Composition. U.S. Patent 9,464,272, filed December 12, 2013, and issued Jun 18, 2015.

**Complete List of Published Work in MyBibliography:**

<https://www.ncbi.nlm.nih.gov/myncbi/malcolm.meyn.1/bibliography/public/>

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors.  
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Sam C. Tetlow

ERA COMMONS USER NAME (credential, e.g., agency login): S.TETLOW

POSITION TITLE: President, Exec Chairman, Amalgent, Inc.

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.*)

| INSTITUTION AND LOCATION   | DEGREE<br>(if applicable) | Completion Date<br>MM/YYYY | FIELD OF STUDY                    |
|--|---------------------------|----------------------------|-----------------------------------|
| Worcester Polytechnic Institute                                  | B.S.                      | 05/1993                    | Aerospace Engineering             |
| The University of North Carolina - Kenan-Flagler Business School | MBA                       | 05/2003                    | Master of Business Administration |

**A. Personal Statement**

**Scientific accomplishments:** Throughout my career I have directed highly efficient multi-disciplinary research and business teams, including a particular focus on novel product development in the molecular, cellular, systems, and computational biology fields. My training has principally been in a company environment and spans from new therapeutic mechanisms to epigenetics, biomarker discovery & validation, diagnostics and device development, as well as clinical drug development. I have contributed significantly over the past 22 years to the field of personalized medicine, including genomics, epigenetics, and proteomics advancement by starting with the first clinically validated biomarkers from the CYP450 family of enzymes that gave rise to a first-in-class warfarin kit in 2002 (2C19/VKORC1) to the development of the first biochemically pure portfolio of recombinant designer nucleosomes in 2016, and most recently in the demonstration of AMGT-0220 in humans showing efficacy and safety for effective analgesic management as a first-in-class adjuvant therapy for pain management upon which this Direct to Phase II grant is based.

As the leader within multiple small business concerns that have received over \$40 million in over 25 SBIR grants, I have led and facilitated Principal Investigators who have received government funding from NINDS, NCI, NICHD, NIBIB, NIH, and State of NC. Crucially, these NIH investments have funded actual product development and the realization of tens of millions of dollars in revenue. In addition, I developed the strategies for strong patent portfolios to secure innovation as the bedrock of these technology based companies.

**Product & business accomplishments:** Since 2001, I have founded and led advanced technology companies that have helped develop the field of knowledge-based healthcare diagnostics and personalized medicine. My key contribution has been the successful longitudinal track-record of translating basic research from an academia and company setting to the development and rollout of viable products that generate growing revenue with a defensible position in a competitive global marketplace. A particular focus has been in the field of new drug development, and I have applied that experience to the development of AMGT-0220. I have worked with most of the major pharma and biotechnology companies as both customers and partners. These companies have contributed revenue, development funds, and co-development projects.

I have a track record of success in product development, team-based execution, and program management, which provides an excellent foundation to deliver success. As co-founder, President, and Executive Chairman of Amalgent, I will oversee the commercialization of AMGT-0220 described in this Fast Track proposal.

Recently completed projects that I would like to highlight:

R44 CA224848

Muller (PI), Role: Co-Investigator

07/18/2018-08/31/2022

Increased sensitivity of minimal residual disease monitoring using peripheral blood in pediatric patients with acute lymphoblastic leukemia

## **B. Positions, Scientific Appointments, and Honors**

### **Positions and Employment**

|              |   |  |
|--------------|---|--|
| 2020-present | Co-founder and Executive Chairman, Amalgent, Inc. | Chapel Hill, NC                        |
| 2013-2022    | Chairman, BioFluidica                             | Research Triangle Park, NC             |
| 2013-2014    | VP Scientific Affairs, BioFluidica                | Research Triangle Park, NC             |
| 2013-2016    | CEO, EpiCypher, Inc                               | Research Triangle Park, NC             |
| 2010-2013    | General Manager, ILS Genomics                     | Research Triangle Park, NC             |
| 2008-2010    | VP Development, Calvert Research                  | Cary, NC                               |
| 2001-2010    | Partner, Research Triangle Ventures               | Raleigh, NC                            |
| 2005-2007    | CEO, Gentrис Corporation                          | Morrisville, NC                        |
| 1993-2000    | Technical Development, General Electric           | Various Locations across US and Global |

### **Honors**

|      |   |
|------|---|
| 2016 | Ethics in Business Award, Rotary Society                                |
| 2016 | CEO of Best University Startup of 2016, United States Congress          |
| 2013 | CBO of ILS, Best Life Sciences Award, Clinical Research Organization    |
| 2003 | Beta Gamma Sigma Honor Society, University of North Carolina            |
| 2003 | Alpha Epsilon Lambda Honor Society, University of North Carolina        |
| 1999 | Recognized in GE Annual Report for technical and business contributions |
| 1993 | Honors Degree, Worcester Polytechnic Institute                          |

### **Board of Directors**

Amalgent, Inc. (2020 to present)

BioFluidica, Inc. Operating (2013 to 2022)

RTP Capital Angel Network. Operating (2014 to present)

EpiCypher, Inc. Operating (2013 to 2016)

ILS Genomics, LLC. Sale of Company to LabCorp (2012 to 2015)

Immunologix, Inc. Sale of Company to Intrexon (2010 to 2011)

Gentrис Corporation. Sale of Company to Cancer Genetics, Inc. (2003 to 2010)

Tranzyme Pharma, Inc. IPO April, 2011 (2003 to 2008)

Noverant, Inc. Sale to Private Party (2003 to 2006)

## **C. Contributions to Science**

- 1) As a founder of Amalgent, I oversaw the pre-launch activities of AMGT-0220 through a grant from the NC Biotechnology Center with the principal investigators, Drs. Brewer and Clemens, and the founding and first equity raise of capital in Amalgent. I realized key inflection points of collaborator engagement, product development, and regulatory, reimbursement and participated in the Series Seed investment in the company.
- 2) As CEO of EpiCypher, I facilitated the development and manufacturing of the first biochemically pure recombinant nucleosome (standard and custom) which supported the first clinically-valid ChIP-seq kit for

quantitative epigenetic biomarker discovery and validation. I raised \$250k equity; \$250k debt and \$3.5 million non-dilutive funding via NIH SBIR program, and I established a cash-flow positive business where revenue doubled each year since inception.

- 3) As Chairman of the Board and VP of Scientific Affairs at BioFluidica, I structured three ground-breaking collaborations to reduce patient burden by translating academic research into a clinical setting to validate the isolation from peripheral blood of circulating Multiple Myeloma cells using immunophenotyping markers CD56 & CD38 with t4:14 chromosome translocation validation; non-small cell lung cancer cells to deliver integrated isolation and PCR of seven validated biomarkers; and monitoring of minimal residual disease for acute myeloid leukemia through isolation of dual cell-types fibroblast activation protein alpha and epithelial cell adhesion molecule. I raised multiple equity rounds totaling \$21 million yielding a 15x increase in valuation, in conjunction with Management. I also secured 6 Ph1 SBIRs and 3 Ph2 SBIRs and played a key role in supporting investor relationships and presentations.
- 4) As Founder and General Manager of ILS Genomics, I identified, negotiated and closed asset purchase from Beckman Coulter Genomics into the newly formed ILS Genomics, LLC. Once closed, I led the organization from zero revenue to a run rate of over \$2 million in the first year reaching profitability and subsequent sale to LabCorp for a 5x return (9/15).
- 5) I have made many additional contributions to numerous entrepreneurial healthcare companies over the past twenty one years, enabling the development and commercialization of novel diagnostics, devices, and therapeutics. These activities include:
  - a. As interim CEO and Board Chair at Gentris, I led due diligence and deal structuring for Series A and facilitated fundraising for Series B and Series C, which I monitored through the sale of the company. I negotiated the successful exit for one of two divisions (8/07) and the sale of the services division to Cancer Genetics, Inc. (6/14).
  - b. Initiating an industry-based development of SWI/SNF nucleosome remodeling assay to deliver a validated detection platform used in drug discovery and development as well as overseeing the development and FDA approval via 510(k) pathway of an early diagnostic assay using validated molecular biomarkers for genomic reference controls (2006) and Coumadin safety profiling (2008).
  - c. Led due diligence and deal structuring for early stage pre Series A convertible note at Respirics, a medical device company which was sold to Hisun Pharmaceuticals (2/12)
  - d. As a Board of Director observer and investor in Tranzyme Pharma, I led due diligence and co-led deal structuring for Series A, continuing with the company through IPO, (12/11)

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors.  
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Brian Spears

eRA COMMONS USER NAME (credential, e.g., agency login): SPEARSB

POSITION TITLE: Associate Medical Director

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.*)

| INSTITUTION AND LOCATION                            | DEGREE<br>(if applicable) | Completion Date<br>MM/YYYY | FIELD OF STUDY                 |
|---|---------------------------|----------------------------|--------------------------------|
| Georgia Institute of Technology, Atlanta, GA        | BS                        | 05/2006                    | Biomedical Engineering, Honors |
| Medical College of Georgia, Augusta, CA             | MD                        | 05/2010                    | Medicine                       |
| University of Alabama at Birmingham, Birmingham, AL | Residency                 | 06/2013                    | Emergency Medicine             |

**A. Personal Statement**

Throughout my career, I have been deeply involved in the design, oversight, and analysis of clinical trials across a broad range of medical fields, including infectious diseases, cardiology, gastroenterology, and more. As the lead investigator in over 40 early-phase trials, I have pioneered efforts to understand drug safety, efficacy, pharmacokinetics, and pharmacodynamics in both healthy and patient populations. My particular focus has been on developing methodologies that not only comply with regulatory standards but also push forward the boundaries of what is possible in drug testing, thereby accelerating the path of new drugs from concept to market.

My extensive background in conducting complex clinical trials has equipped me with a unique perspective and skill set that make me an effective leader in pharmaceutical research and development. This first-in-class pain medication described in this SBIR Fast Track proposal exemplifies my strategic vision and dedication to addressing the urgent needs presented by the ongoing opioid crisis, potentially revolutionizing pain management and offering new hope to thousands suffering from chronic pain.

**B. Positions, Scientific Appointments, and Honors****Positions**

|                |   |
|----------------|---|
| 2021 – Present | Associate Medical Director, Clinical Research Unit, PPD, Austin, TX                       |
| 2015 – Present | Medical Director, USACS-Emergency Medicine Physician, Lakeway, TX                         |
| 2016 – 2020    | Part Owner/Investor, Physicians Premier ER, Emergency Medicine Physician, San Antonio, TX |
| 2014 – 2015    | Emergency Medicine Physician, EMCARE, San Antonio, TX                                     |
| 2013 – 2014    | Emergency Medicine Physician, Level V Healthcare, San Antonio, TX                         |
| 2010 – 2013    | Resident Physician, University of Alabama at Birmingham, Birmingham, AL                   |
| 2012 – 2013    | Physician, Northwest Medical Center, Winfield, AL   |
| 2011 – 2012    | Physician, American Family Care, Birmingham, AL   |

**C. Contributions to Science**

Over my 12 year career, I have contributed to over 40 clinical drug trials covering safety, tolerability, and pharmacokinetics for drug candidates being developed for treating an array diseases and conditions from infectious diseases to neurological indications. Examples of this work are presented below.

**1. Innovative Approaches in Neurology and Mental Health Studies.** Through my leadership in designing and administering randomized, double-blind, and placebo-controlled studies, I have explored safety and efficacy of novel neurologic and psychiatric treatments. These include modified release tablets and the systemic evaluation of food effects on drug absorption, which have advanced our understanding of drug interactions and metabolic processes critical for treating neurological disorders and mental health conditions.

- a) Neurology: A Phase 1, Randomized, Open-Label Trial to Evaluate the Pharmacokinetics, Relative Bioavailability, Safety, Tolerability, and Food Effect of 2 Study Drug Modified Release Tablet Formulations in Healthy Adults.
- b) Neurology: A Phase 1, Randomized, Double-Blind, Placebo-Controlled Single Ascending Dose Study in Healthy Subjects to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Study Drug in Conjunction with an Evaluation of the Effect of Food on Study Drug Pharmacokinetics
- c) Mental Health: An Ascending, Single Oral Dose, Double-Blind, Randomized, Placebo-Controlled Study To Assess The Safety, Tolerability, And Pharmacokinetics Of study drug In Fasted Healthy Adult Male And Female Subjects (Part A) And Open-Label Single Oral Dose Administered With And Without Food (Part B).
- d) Central nervous system: A Phase 1 Dose Escalation Study in Healthy Subjects to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Study Drug, the Effect of Food and Formulation on Study Drug Kinetics, and CYP3A-Mediated Drug-Drug Interactions with Study Drug

**Pharmacological Intervention in Infectious Diseases.** I have significantly contributed to the understanding and enhancement of pharmacological approaches in infectious diseases. This includes partaking in various Phase 1 studies to evaluate the safety, tolerability, and pharmacokinetics of innovative treatments, such as monoclonal antibodies and long-acting drug formulations. These studies have helped facilitate the development of treatments that offer improved patient outcomes, particularly in fields burdened by limited therapeutic advancements.

- a) A Phase 1, Single-Arm, Open-Label Study to Assess the Safety and Tolerability of Study Drug in Combination with an Oral Contraceptive Containing Ethinyl Estradiol and Levonorgestrel in Healthy Premenopausal Female Subjects.
- b) A Phase 1, Open-Label, Single-Dose Study of the Safety and Pharmacokinetics of a Human Monoclonal Antibody, Study Drug, Administered Subcutaneously with Study Drug to Healthy Adults.
- c) A Phase I, Multi-Centre, Open-Label, Single Dose Escalation Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Long-Acting Study Drug Co-Administered with Study Drug in Healthy Adult Volunteers.

**2. Pioneering Studies in Cardiovascular and Gastrointestinal Therapeutics.** My involvement in conducting crossover comparative studies and pharmacodynamic evaluations in healthy subjects has helped shape the testing and validation of cardiovascular and gastrointestinal medications. My effective coordination of trials on aspirin injections, tablets, and other drug formulations has ensured reliable data on drug efficacy and safety, useful in clinical applications for related diseases.

- a) A Phase 1, Open-Label, 2-Period, 2-Formulation, Within-Subject Crossover Comparative Pharmacokinetic, Pharmacodynamic, And Safety Study Of 1 Dose Level Of Aspirin For Injection And Oral Aspirin Tablets In Healthy Adult Human Subjects Under Fasting Conditions.
- b) A Phase 1 Study in Healthy Subjects to Evaluate the Bioavailability of Risankizumab 150 mg/ml Formulation in the 180 mg Prefilled Syringe Relative to 90 mg/ml Formulation in the 90 mg Prefilled Syringe.

**4. Groundbreaking Drug Interactions and Pharmacokinetics in Urology.** In the field of urology, my efforts have centered on methodologically robust Phase 1 trials that assess the pharmacokinetic profiles, safety, and efficacy of new drugs intended for the treatment of urinary tract infections and other urological conditions. These studies have provided key insights into drug-disease interactions which are pivotal for developing targeted therapies.

- Urology: A Phase III, Randomized, Multicenter, Parallel-Group, Double-Blind, Double-Dummy Study in Adolescent and Adult Female Participants Comparing the Efficacy and Safety of Study Drug to Study Drug in the Treatment of Uncomplicated Urinary Tract Infection (Acute Cystitis).
- Urology: A Phase 1 Randomized, Double-blind, Placebo-controlled, Single and Multiple Ascending Dose and Food Effects Study of the Safety, Tolerability, and Pharmacokinetics of study drug in Healthy Subjects.

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors.  
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Charles E. Argoff

ERA COMMONS USER NAME (credential, e.g., agency login): ARGOFFCE

POSITION TITLE: Professor of Neurology, Albany Medical College

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.*)

| INSTITUTION AND LOCATION                            | DEGREE<br>(if applicable) | Completion Date<br>MM/YYYY | FIELD OF STUDY                         |
|---|---------------------------|----------------------------|--|
| Northwestern University, Evanston, IL               | BMS                       | 06/1982                    | Honors Program in Medical Education    |
| Northwestern University Medical School, Chicago, IL | MD                        | 06/1984                    | Honors Program in Medication Education |

**A. Personal Statement**

With a career dedicated to advancing the understanding and management of pain, particularly neuropathic pain, I bring a wealth of experience and a track record of leadership in both clinical and academic settings. My work at Albany Medical College, where I serve as Professor of Neurology and Director of the Comprehensive Pain Center, underscores my commitment to improving patient outcomes through innovative treatment strategies and education. My research interests, particularly in the repurposing of existing medications for pain management, align closely with the aims of Amalgent Therapeutics' project to develop safer opioid alternatives. I have led numerous clinical trials, contributing to the body of evidence supporting new pain management approaches. My leadership roles in professional societies and editorial contributions to medical journals further demonstrate my influence in the field. These experiences underscore my deep involvement in enhancing pain management therapies through innovative research, clinical application, educational leadership, and regulatory guidance, directly aligning with the goals of developing safer and more effective pain management options in SBIR projects. I am excited about the potential to contribute to a project that aligns so closely with my professional mission to mitigate the impact of chronic pain on individuals' lives.

**B. Positions, Scientific Appointments, and Honors****Positions**

|                |   |
|----------------|---|
| 2024 – Present | Consultant, Amalgent Therapeutics, Chapel Hill, NC  |
| 2021 – Present | Vice Chair, Department of Neurology, Albany Medical Center, Albany, NY  |
| 2016 – Present | Director, ACGME Accredited Pain Management Fellowship, Albany Medical College, Albany, NY   |
| 2011 – 2012    | Consultant/Medical Director, Asante Communications, New York, NY  |
| 2007 – Present | Professor of Neurology, Attending Physician and Director, Comprehensive Pain Center, Albany Medical College, Albany, NY                         |
| 2007 – 2011    | Consultant/Medical Director, McMahon Publishing Group, New York, NY   |
| 1992 – 2007    | Attending Physician, Director, Cohn Pain Management Center, Department of Neurology, North Shore University Hospital, Manhasset and Syosset, NY |
| 1992 – 2000    | Co-Founder, Pain Medicine Consultant, Pain Management Associates of St. John's, Smithtown, NY   |
| 1992 – 1995    | Director, Neurologic Rehabilitation, North Shore University Hospital, Manhasset, NY   |
| 1992 – 1995    | Deputy Chairman, Department of Neurology, North Shore University Hospital, Manhasset, NY  |
| 1991 – 1992    | Chief of Neurology, Northport VAMC, Northport, NY   |

|             |   |
|-------------|---|
| 1991 – 1992 | Attending Neurologist, Stony Brook University Hospital, Stony Brook, NY         |
| 1990 – 1991 | Assistant Director, Pain Program, Spaulding Rehabilitation Hospital, Boston, MA |

### **Honors**

|      |  |
|------|--|
| 2019 | Presidential Commendation, American Academy of Pain Medicine                               |
| 2018 | Presidential Commendation, American Academy of Pain Medicine                               |
| 2016 | John Bonica Award and Lecture for contributions to Pain Medicine, Eastern Pain Society     |
| 2014 | Distinguished Service Award, American Academy of Pain Medication                           |
| 2013 | Honorary Chairperson/Speaker US Pain Foundation Gala                                       |
| 2012 | Elizabeth Narcessian Award for Outstanding Educational Achievements, American Pain Society |
| 2011 | Academic Pain Educator of the Year Award, American Society of Pain Educators               |
| 1990 | Young Investigator Travel Award  |

### **C. Contributions to Science**

- 1. Expertise in Opioid Management and Development of Novel Pain Therapies.** I have extensively studied and contributed to the sector of pain management, particularly focusing on opioid alternatives and novel therapeutic strategies. My comprehensive investigation into alternative pain management mechanisms has paved the way for advancements in clinical applications, reducing opioid dependency. A notable contribution is my involvement in the clinical development and study of various alternative pain management therapies, which are crucial for establishing more effective and safer pain treatment protocols.
  - Peppin JF, Albrecht PJ, **Argoff C**, et al. "Skin Matters: A Review of Topical Treatments for Chronic Pain. Part Two: Treatments and Applications." *Pain Ther*. 2015 Jun;4(1):33-50.
  - Argoff CE**, et al. "Pain Management and Opioid Therapy: Persistent Knowledge Gaps Among Primary Care Providers." *J Pain Res*. 2021 Oct 11;14:3223-3234.
  - Petersen EA, Stauss TG, Sowcroft JA, et al. "Durability of High-Frequency 10-kHz Spinal Cord Stimulation for Patients With Painful Diabetic Neuropathy: 12-Month Results From a Randomized Controlled Trial." *Diabetes Care*. 2022 Jan 1;45(1):e3-e6.
- 2. Implementation and Optimization of Clinical Protocols in Pain Management.** My leadership roles, including my directorship at the Comprehensive Pain Center, allowed me to influence and reshape clinical protocols significantly. Under my guidance, pain management strategies were refined, leading to optimized patient outcomes and enhanced safety protocols, critical for developing regulatory-compliant clinical strategies within SBIR projects.
  - Lee JH, Koutalianos EP, Leimer EM, Bhullar RK, **Argoff CE**. "Intravenous Lidocaine in Chronic Neuropathic pain: A Systematic Review." *Clin J Pain*. 2022 Dec 1;38(12):739-748.
  - Staudt MD, Prabhala T, Sheldon BL, et al. "Current Strategies for the Management of Painful Diabetic Neuropathy." *J Diabetes Sci Technol*. 2022 Mar;16(2):341-352.
- 3. Educational Leadership and Development of Pain Management Guidelines.** I have directed numerous educational courses and workshops that have standardized pain management teachings at both national and international levels. These endeavors have been crucial in disseminating up-to-date, evidence-based pain management practices, aiding in the formulation of both educational material and guidelines that inform clinical strategy and product label design in pain management.
  - Argoff CE**, et al. "Fundamentals of Pain Management for residents and fellows, sponsored by the American Pain Society." Presented at the Annual Scientific Meeting.
- 4. Interdisciplinary Approaches to Pain Management.** Through my career, I have fostered interdisciplinary collaboration between pharmacology, neurology, and regulatory sciences, enriching the clinical approach to pain management. This multidisciplinary approach is critical for the effective translation of clinical trial results into marketable products, ensuring that all stakeholder perspectives are considered in product development and label design.

- a. Wahezi SE, Duarte R, Kim C, et al. "An Algorithmic Approach to the Physical Exam for the Pain Medicine Practitioner: A Review of the Literature with Multidisciplinary Consensus." *Pain Med.* 2022 Aug 31;23(9):1489-1528.
  - b. Shao MM, Khazen O, Hellman A, Czerwinski M, Dentinger R, DiMarzio M, et al. "Effect of First-Line Ziconotide Intrathecal Drug Therapy for Neuropathic Pain on Disability, Emotional Well-Being, and Pain Catastrophizing." *World Neurosurg.* 2021 Jan;145:e340-e347.
5. **Development of Regulatory Strategies for Pain Management.** My role in various national committees, including involvement with FDA patient safety workgroups, has enabled me to contribute significantly to shaping the regulatory landscape of pain management. This experience is invaluable in navigating the complex regulatory requirements for SBIR projects aimed at introducing new pain management therapies.
- a. Covington EC, **Argoff CE**, Ballantyne JC, et al. "Ensuring Patient Protections When Tapering Opioids: Consensus Panel Recommendations." *Mayo Clin Proc.* 2020 Oct;95(10):2155-2171.

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors.  
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Klein, Gerald L.

eRA COMMONS USER NAME (credential, e.g., agency login): GERRYKLEIN

POSITION TITLE: Principal, MedSurgPI

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.*)

| INSTITUTION AND LOCATION        | DEGREE<br>(if applicable) | Completion Date<br>MM/YYYY | FIELD OF STUDY                         |
|---------------------------------|---------------------------|----------------------------|--|
| University of Florida           | BS                        | 06/1969                    | Psychology                             |
| Vrije Universiteit Brussel      | MD                        | 06/1975                    | Medicine                               |
| Rutgers Medical School          | Other training            | 06/1977                    | Pediatrics Residency                   |
| University of California Irvine | Other training            | 06/1979                    | Allergy/Clinical Immunology Fellowship |

**A. Personal Statement**

With a robust foundation in drug development and a proven history of obtaining FDA and EU endorsements for pharmaceuticals, I am exceptionally qualified for the Chief Medical Officer position within Amalgent's pain medication initiative. My innovative leadership in the biopharmaceutical sector is marked by a unique proficiency in fostering client relationships and steering them through the complexities of both development and market introduction. My global expertise encompasses the entire spectrum from preclinical research of biologics, devices, diagnostics, and drugs to conducting post-marketing studies. In my current role as Principal at MedSurgPI, I leverage extensive knowledge in medical affairs, clinical development, and medical monitoring. My industry journey commenced as a Principal Investigator, leading a multitude of clinical trials across various therapeutic domains. Subsequently, I established the San Diego Clinical Research Association (SDCRA), a Site Management Organization (SMO) and Contract Research Organization (CRO), where I held the positions of CEO and CMO. Under my leadership, SDCRA executed studies in a wide array of medical fields, culminating in its acquisition by Quintiles (now IQVIA). As a Senior Vice President at IQVIA, I contributed significantly to Global Drug Development and Medical Affairs. Furthermore, I am a pioneer in the industry, having founded Pathway Diagnostic, Klein Medical News Service, Entera and Health, and holding executive roles such as CEO, CMO, SVP, and VP in Medical and Clinical Affairs at esteemed organizations like Dey/MerckKgAa, Specialty Labs, Talecris/Grifols, Oxygen Biotherapeutics/Tanex, and Pathway Diagnostics. My consultancy as CMO for biotech firms such as Aruna and Belhaven, alongside my active participation on the Board of Directors for several biotech entities, underscores my commitment and influence in the field. My academic training allows me to contribute the necessary pediatrics expertise to this project. As an Allergist and Clinical Immunologist, I hold an Adjunct Professorship in the Department of Pharmacology, Brody School of Medicine at East Carolina University. Previously, I enriched the Division of Basic and Applied Immunology at the University of California, Irvine, as a Professor of Medicine and Pediatrics. My role as an associate editor and board member for several esteemed publications, coupled with a comprehensive portfolio of peer-reviewed articles, underscores my commitment to medical scholarship. This blend of academic prowess and industry acumen positions me to excel in the role of Chief Medical Officer for Amalgent's pain medication development program.

Publications that I would like to highlight include:

1. **Klein GL**, How to More Objectively Assess Adverse Event Causality in a Clinical Trial. SOCRA Source. Aug 2024; 79-84.
2. **Klein GL**, Morgan RE, Zhang S, Vaezzadeh S, and et al. Improving Informed Consent Forms (ICFs) in Clinical Trials, Especially for Vulnerable Populations, A Global Need. Poster presented at: Society for Clinical Research Associates; Montreal, Canada; Sept 28, 2023.
3. **Klein GL**, and Morgan R. Potential Errors and Corrections in Early Phase Drug Development. Clin Trial Pract Open J. 2022. 5(1): 1-5.
4. Taskin D, Klein GL, Coleman S. and et al: Comparing COPD Treatment: Nebulizer, Metered Dose Inhaler, and Concomitant Therapy. 2007. Am J Med 120(5):435-41

## **B. Positions, Scientific Appointments, and Honors**

### **Positions and Scientific Appointments**

- 2023 - present Adjunct Professor of Pharmacology and Toxicology in Brody School of Medicine at East Carolina University
- 2015 - present Principal, MedSurgPI, LLC / Raleigh, NC
- 2012 - 2015 President and CEO, Entera Health, Inc / Cary, NC
- 2011 - 2012 Chief Medical Officer / Oxygen Biotherapeutics, Durham, NC
- 2010 - 2011 Consulting Chief Medical Officer / Telacris Biotherapeutics / Grifols
- 2010 - 2011 Board Member, Oxygen Biotherapeutics (Tenax Therapeutics) (NASDX)
- 2009 - 2011 Board Member, Nano Corp Therapeutics
- 2005 - 2010 Chief Medical Officer, VP Global Medical & Clinical Affairs, Talecris Biotherapeutics, Durham, NC
- 2003 - 2005 Vice President of Medical Affairs / Clinical Research and Safety at Dey/Merck KGaA
- 2003 - 2005 Adjunct Professor Pharmaceutics and Medicinal Chemistry at the Henry T. Long School of Pharmacy and Health Sciences at University of the Pacific
- 2003 - 2005 Allergist, North Bay Allergy and Asthma Associates, Napa, CA
- 2002 - 2003 Vice President of Clinical Trials / Specialty Laboratories/Founder EVP Pathway Diagnostics
- 2002 - 2002 Executive Vice President, Clinical Development and Medical Affairs / Clingenix, Inc., San Diego, CA
- 2000 - present Board Member, Plakous Therapeutics
- 1998 - 2002 Senior Vice President, Executive Director / Infectious Allergy, and Respiratory Disease /Quintiles Transnational, Raleigh, NC
- 1988 - 1998 Founder, CEO and President / San Diego Clinical Research Associates (SDCRA) (CRO) San Diego, CA
- 2010 - 2011 Board Member, Oxygen Biotherapeutics (Tenax Therapeutics) (NASDX)
- 2009 - 2011 Board Member, Nano Corp Therapeutics
- 1988 - 1998 Board Member, San Diego Clinical Research Associates, Inc. (CRO)
- 1984 - 1988 Board Member, American College of Allergy and Clinical Immunology
- 1989 - 2003 Professor of Clinical Medicine and Pediatrics, Dept of Basic and Applied Immunology, University of California, Irvine, CA
- 1984 - 1989 Associate Professor of Clinical Med and Ped, University of California, Irvine
- 1979 - 1984 Assistant Clinical Professor of Med and University of California, Irvine
- 1979 - 1980 Assistant Director of the Adult Allergy Clinic University of California, Irvine
- 1980 - 1989 Assistant Clinical Professor of Pediatrics, University of California, San Diego
- 1979 - 1998 Founder and Sr. Partner / Allergy Immunology Medical Group / Vista, CA

### **Honors**

- 1987 - 1988 American College of Allergy & Clinical Immunology Executive Cmte, Board of Regents Joint Council of Allergy Education Committee Member
- 1986 Volunteer Faculty Member of the Year Nominee, University of California, Irvine
- 1986 American College of Allergy & Clinical, Immunology Alternate Delegate, House of Delegates
- 1986 American Association for Clinical Immunology and Allergy, Representative Speaker on Lifetime Cable TV

|             |   |
|-------------|---|
| 1985        | American Board of Allergy & Immunology Review Course, Appointed to Faculty  |
| 1984 - 1988 | American College of Allergy Asthma and Clinical Immunology, Board of Regents  |
| 1984        | American Assoc. for Clinical Immunology and Allergy, Chairman   |
|             | Joint Council of Allergy Education Committee Member   |
| 1979        | Accepted for presentation of the 1979 National Student Research Forum:<br>Theophylline-Induced Suppression of T Cells Bearing IgM |

### C. Contributions to Science

1. **Medical monitoring of drug development clinical trials.** Developed quality systems to improve clinical trials
  - a. **Klein GL.** How to More Objectively Assess Adverse Event Causality in a Clinical Trial. SOCRA Source. Aug 2024; 79-84.
  - b. **Klein GL**, Morgan R, and Johnson PC. Medical Monitoring in Clinical Trials. *J Clin Trials*. Jan 2021
  - c. Li H, Vaughan L, Hanna K, **Klein G**, Petteway S. Applying quality audit principles in managing quality of clinical documents. *Quality Assurance Journal*. 2009; 12:S40.
  - d. Li H, Hawk S, Hanna K, **Klein G**, and Petteway S. Developing and Implementing a Comprehensive Clinical QA Audit Program. *Qual Assur J* 2007; 11, 128–137.
2. **Economic and clinical outcome risk assessment and mitigation in clinical practice:** Developed pharmacoeconomic studies to help decrease costs in clinical practice.
  - a. **Klein G** and Clarke M. The Pharmacy Adjudicated Clinical Study Supply Process Decreases Risk, Cuts the Cost and Improves the Efficiency when Providing Subjects Unblinded Clinical Study Supplies, *Journal for Clinical Studies*, June 1, 2017
  - b. Shafran I, Youong H, Burgunder P and **Klein GL**. Pharmacoeconomic benefit of bovine serum immunoglobulin in inflammatory bowel disease. *Advance in Gastroenterology*. January 2016
  - c. York J. and **Klein GL**. An exploratory economic evaluation of chronic obstructive pulmonary disease (COPD) patients on combination product versus individual components (ipratropium bromide and albuterol) *Advances in Therapy* 2007
3. **Pediatric allergy and immunologic disease:** Improving the practical pediatric treatment of allergic disorders and its complications.
  - a. **Klein GL.** Non-Prescription Brompheniramine Maleate Versus Terfenadine in Treating Symptomatic Allergic Rhinitis, 1996.
  - b. **Klein GL**, Ziering RW. Improving the Pharmacological Treatment of the Young Child with Asthma and Allergies, *Immunol. Practical Allergy*, May, 1983.
  - c. **Klein GL**, Ziering RW. Obstructive Sleep Apnea Presenting as Mouth Breathing in a Five Year Old, *Immunol. Allergy Pract.*, 6:9, 1984.
  - d. **Klein GL.** Problems with the Use of Inhaled Medication in the School System, *Amer. J. Asthma Allergy Pediatricians*, Vol. II, Oct., 1989.

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors.  
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Timothy R. Wright

ERA COMMONS USER NAME (credential, e.g., agency login): TIMWRIGHT

POSITION TITLE: Strategic Advisor

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.*)

| INSTITUTION AND LOCATION            | DEGREE<br>(if applicable) | Completion Date<br>MM/YYYY | FIELD OF STUDY |
|-------------------------------------|---------------------------|----------------------------|----------------|
| Ohio State University, Columbus, OH | BSc                       | 05/1981                    | Marketing      |

**A. Personal Statement**

As a seasoned executive with over 30 years of experience in the pharmaceutical, biotech, and medical devices industries, I have dedicated my career to transforming organizations and driving growth and profitability in highly competitive markets. My leadership in successful turnarounds, including the formation of DuPont-Merck Pharma and my tenure as President at Elan Biopharma, underscores my ability to navigate and lead through complex challenges. My work at Covidien Mallinckrodt, focusing on pharmaceutical products and imaging solutions, further exemplifies my commitment to innovation and patient-centered care. I am particularly proud of my role in re-establishing credibility with the FDA and raising significant capital to advance organizational missions. My vision for the future includes leveraging my extensive experience in drug development, regulatory affairs, and strategic partnerships to contribute to groundbreaking projects like Amalgent Therapeutics' development of a first-in-class pain medication. This initiative aligns with my lifelong mission to improve health outcomes and quality of life through innovative care, making me an ideal candidate to lead efforts in addressing the opioid crisis with safer, effective pain management solutions.

**B. Positions, Scientific Appointments, and Honors****Positions**

- 2024 – Present Strategic Advisor, Amalgent Therapeutics, Chapel Hill, NC
- 2010 – Present Founder/Partner & Chief Executive Officer, Signal Hill Advisors
- 2022 – 2023: Chairman of The Board of Directors, Isosceles Pharmaceuticals
- 2019 – 2022: Chief Executive Officer, MiMedx, Marietta, Georgia, United States
- 2017 – 2019: President and Chief Executive Officer, M2GEN, Tampa, Florida, United States
- 2015 – 2017: Executive Vice President Corporate Strategy, Global Business Development and Innovation, Teva Pharmaceuticals, Cambridge, Massachusetts, United States
- 2011 – 2015: President – Ohio State Innovation Foundation, The Ohio State University, Comprehensive Cancer Center, Columbus, Ohio
- 2007 – 2010: President / CEO – Pharmaceuticals and Medical Imaging, Mallinkrodt Covidien, St. Louis, Missouri
- 2004 – 2007: Interim CEO / President / Chief Operating Officer / Board Member, AAI Pharma, Wilmington, North Carolina
- 2001 – 2004: EVP (2001-2002) / President (2001-2004), Elan Pharmaceuticals, Dublin, Ireland & San Diego, California
- 1999 – 2000: Senior Vice President of Healthcare Product Services, Cardinal Health, Dublin, Ohio, United States

1984 – 1999: Senior Vice President, Strategy & Corporate Business Development, Dupont Merck Pharmaceutical Company, Wilmington, Delaware

### Honors

2022: CEO of the Year, PM360  
2020: PM360 ELITE Transformational Leader

### C. Contributions to Science

- 1. Leadership in Pharmaceutical and Biotechnological Innovations.** I have been in transformative leadership across various roles in the pharmaceutical and biotech industries. At MiMedx, as Chief Executive Officer, I spearheaded a significant organizational turnaround by focusing on product innovation, patient care, integrity, and the reestablishment of FDA credibility with rigorous compliance and transparency in operations. This strategic insight into regulatory pathways and commitment to therapeutic innovation is crucial for advancing novel clinical strategies in drug development.
  - a. Rebuilt the senior leadership team at MiMedx, focusing on product innovation and patient care.
  - b. Successfully settled major legal challenges, including SEC and DOJ settlements.
  - c. Hosted capital raises of over \$150M and achieved NASDAQ registration, demonstrating effective fiscal oversight and investor confidence.
- 2. Strategic Development and Management of International Pharmaceutical Operations.** As Executive Vice President at Teva Pharmaceuticals, I played an integral role in global strategic planning, business development, and innovation. I managed comprehensive aspects of pharmaceutical operations, including strategic mergers and acquisitions, such as the \$3.2B acquisition of Rimsa and forming strategic international partnerships, including a joint venture with Takeda in Japan. These experiences underscore my ability to navigate complex international market dynamics and regulatory environments, which are essential for the development and commercialization of new drug products.
  - a. Led strategic partnerships and mergers, notably the \$3.2B acquisition of Rimsa and a joint venture with Takeda.
  - b. Managed the divestiture process delivering \$3.2B in proceeds, demonstrating exceptional strategic and financial stewardship.
- 3. Pioneering Personalized Medicine and Healthcare Informatics.** As President and CEO of M2GEN, I directed the operational strategy and scaling of a health informatics company that enhances personalized medicine through the Oncology Research Information Exchange Network (ORIEN). My leadership in integrating data science with clinical applications highlights my forward-thinking approach to biomedical research, providing a robust model for managing and utilizing big data in clinical trial design and personalized medicine.
  - a. Restructured the Board of Directors and secured a significant capital infusion of \$75M from the Hearst Corporation.
  - b. Expanded the pharmaceutical client base by 25%, demonstrating effective commercial and strategic growth.
- 4. Enhancing Drug Discovery and Development through Cross-Sector Collaboration.** My role as President of the Ohio State Innovation Foundation and leadership positions at The Ohio State University Comprehensive Cancer Center involved strategic oversight of technology commercialization and early-stage drug development enterprises. My efforts in securing funding and managing intellectual property effectively bridged academia, clinical research, and industrial applications, facilitating the translation of innovative research into viable therapeutic products.
  - a. Secured \$25M in funding to support early-stage drug development in oncology and infectious diseases.
  - b. Operationalized the Ohio State Innovation Foundation to manage valuable intellectual properties and foster drug discovery.

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 1

**UEI\*:** CP5VN4N2MXX3

**Budget Type\*:**     Project     Subaward/Consortium

**Enter name of Organization:** AMALGENT THERAPEUTICS, INC.

**Start Date\*:** 04-01-2025

**End Date\*:** 09-30-2025

**Budget Period:**

### A. Senior/Key Person

| Prefix | First Name* | Middle Name | Last Name* | Suffix | Project Role* | Base Salary (\$) | Calendar Months |        |        | Academic Months | Summer Months | Requested Salary (\$)* | Fringe Benefits (\$)* | Funds Requested (\$)* |
|--------|-------------|-------------|------------|--------|---------------|------------------|-----------------|--------|--------|-----------------|---------------|------------------------|-----------------------|-----------------------|
|        |             |             |            |        |               |                  | Months          | Months | Months |                 |               |                        |                       |                       |
| 1.     | Malcolm     | A           | Meyn       |        | PD/PI         | 180,000.00       | 2.4             |        |        | 36,000.00       | 7,200.00      |                        |                       | 43,200.00             |
| 2.     | Sam         |             | Tetlow     |        | Co-I          | 180,000.00       | 0.48            |        |        | 7,200.00        | 1,440.00      |                        |                       | 8,640.00              |

## Total Funds Requested for all Senior Key Persons in the attached file

**Additional Senior Key Persons:** File Name: **Total Senior/Key Person** **51,840.00**

## B. Other Personnel

| Number of Personnel* | Project Role*                       | Calendar Months | Academic Months | Summer Months | Requested Salary (\$)* | Fringe Benefits*                                     | Funds Requested (\$)* |
|----------------------|-------------------------------------|-----------------|-----------------|---------------|------------------------|--|-----------------------|
|                      | Post Doctoral Associates            |                 |                 |               |                        |  |                       |
|                      | Graduate Students                   |                 |                 |               |                        |  |                       |
|                      | Undergraduate Students              |                 |                 |               |                        |  |                       |
|                      | Secretarial/Clerical                |                 |                 |               |                        |  |                       |
| <b>0</b>             | <b>Total Number Other Personnel</b> |                 |                 |               |                        | <b>Total Other Personnel</b>                         | <b>0.00</b>           |
|                      |                                     |                 |                 |               |                        | <b>Total Salary, Wages and Fringe Benefits (A+B)</b> | <b>51,840.00</b>      |

### **RESEARCH & RELATED Budget {A-B} (Funds Requested)**

**RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 1**

UEI\*: CP5VN4N2MXX3

Budget Type\*:  Project  Subaward/Consortium

Organization: AMALGENT THERAPEUTICS, INC.

Start Date\*: 04-01-2025

End Date\*: 09-30-2025

Budget Period: 1

| <b>C. Equipment Description</b>                                     |                        | <b>Funds Requested (\$)*</b> |
|---|------------------------|------------------------------|
| List items and dollar amount for each item exceeding \$5,000        |                        |                              |
| Equipment Item  |                        |                              |
| Total funds requested for all equipment listed in the attached file |                        |                              |
|   | <b>Total Equipment</b> | <b>0.00</b>                  |
| Additional Equipment: File Name:                                    |                        |                              |

| <b>D. Travel</b>   |                          | <b>Funds Requested (\$)*</b> |
|--|--------------------------|------------------------------|
| 1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions) |                          |                              |
| 2. Foreign Travel Costs  |                          |                              |
|  | <b>Total Travel Cost</b> | <b>0.00</b>                  |

| <b>E. Participant/Trainee Support Costs</b> |  | <b>Funds Requested (\$)*</b> |
|---|--|------------------------------|
| 1. Tuition/Fees/Health Insurance            |  |                              |
| 2. Stipends                                 |  |                              |
| 3. Travel                                   |  |                              |
| 4. Subsistence                              |  |                              |
| 5. Other:                                   |  |                              |
| <b>Number of Participants/Trainees</b>      | <b>Total Participant Trainee Support Costs</b> | <b>0.00</b>                  |

RESEARCH &amp; RELATED Budget {C-E} (Funds Requested)

## RESEARCH &amp; RELATED BUDGET - SECTIONS F-K, Budget Period 1

UEI\*: CP5VN4N2MXX3

Budget Type\*:  Project  Subaward/Consortium

Organization: AMALGENT THERAPEUTICS, INC.

Start Date\*: 04-01-2025

End Date\*: 09-30-2025

Budget Period: 1

| F. Other Direct Costs                     |  | Funds Requested (\$)* |
|---|--|-----------------------|
| 1. Materials and Supplies                 |  | 5,000.00              |
| 2. Publication Costs                      |  | 55,500.00             |
| 3. Consultant Services                    |  |                       |
| 4. ADP/Computer Services                  |  | 226,900.00            |
| 5. Subawards/Consortium/Contractual Costs |  |                       |
| 6. Equipment or Facility Rental/User Fees |  | 0.00                  |
| 7. Alterations and Renovations            |  |                       |
| 8. Data Management and Sharing Costs      |  |                       |
| 9. Technical Assistance                   |  | 6,500.00              |
| Total Other Direct Costs                  |  | 293,900.00            |

| G. Direct Costs               |  | Funds Requested (\$)* |
|-------------------------------|--|-----------------------|
| Total Direct Costs (A thru F) |  | 345,740.00            |

| H. Indirect Costs   |  | Indirect Cost Rate (%) | Indirect Cost Base (\$) | Funds Requested (\$)* |
|---|--|------------------------|-------------------------|-----------------------|
| Indirect Cost Type  |  |                        |                         |                       |
| 1 . MTDC  |  | 25.0                   | 137,340.00              | 34,335.00             |
| Total Indirect Costs  |  |                        |                         | 34,335.00             |
| Cognizant Federal Agency<br>(Agency Name, POC Name, and POC Phone Number) |  |                        |                         |                       |

| I. Total Direct and Indirect Costs                    |  | Funds Requested (\$)* |
|---|--|-----------------------|
| Total Direct and Indirect Institutional Costs (G + H) |  | 380,075.00            |

| J. Fee |  | Funds Requested (\$)* |
|--------|--|-----------------------|
|        |  | 26,150.00             |

| K. Total Costs and Fee |  | Funds Requested (\$)* |
|------------------------|--|-----------------------|
|                        |  | 406,225.00            |

|                          |   |
|--------------------------|---|
| L. Budget Justification* | File Name:<br>BudJust_merged_AT_FT_2024.09.03v2.pdf |
|--------------------------|---|

RESEARCH &amp; RELATED Budget {F-K} (Funds Requested)

## RESEARCH &amp; RELATED BUDGET - SECTION A &amp; B, Budget Period 2

UEI\*: CP5VN4N2MXX3

Budget Type\*:  Project  Subaward/Consortium

Enter name of Organization: AMALGENT THERAPEUTICS, INC.

Start Date\*: 10-01-2025

End Date\*: 09-30-2026

Budget Period: 2

## A. Senior/Key Person

|    | Prefix First Name* | Middle Name | Last Name* | Suffix | Project Role* | Base        | Calendar | Academic | Summer | Requested    | Fringe         | Funds Requested (\$)* |
|----|--------------------|-------------|------------|--------|---------------|-------------|----------|----------|--------|--------------|----------------|-----------------------|
|    |                    |             |            |        |               | Salary (\$) | Months   | Months   | Months | Salary (\$)* | Benefits (\$)* |                       |
| 1. | Malcolm            | A.          | Meyn       |        | PD/PI         | 180,000.00  | 6.0      |          |        | 90,000.00    | 18,000.00      | 108,000.00            |
| 2. | Sam                | C.          | Tetlow     |        | Co-I          | 180,000.00  | 1.2      |          |        | 18,000.00    | 3,600.00       | 21,600.00             |

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name: Total Senior/Key Person **129,600.00**

## B. Other Personnel

| Number of Personnel* | Project Role*                       | Calendar Months | Academic Months | Summer Months | Requested Salary (\$)* | Fringe Benefits*                                     | Funds Requested (\$)* |
|----------------------|-------------------------------------|-----------------|-----------------|---------------|------------------------|--|-----------------------|
|                      | Post Doctoral Associates            |                 |                 |               |                        |  |                       |
|                      | Graduate Students                   |                 |                 |               |                        |  |                       |
|                      | Undergraduate Students              |                 |                 |               |                        |  |                       |
|                      | Secretarial/Clerical                |                 |                 |               |                        |  |                       |
| <b>0</b>             | <b>Total Number Other Personnel</b> |                 |                 |               |                        | <b>Total Other Personnel</b>                         | <b>0.00</b>           |
|                      |                                     |                 |                 |               |                        | <b>Total Salary, Wages and Fringe Benefits (A+B)</b> | <b>129,600.00</b>     |

RESEARCH &amp; RELATED Budget {A-B} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 2**

UEI\*: CP5VN4N2MXX3

Budget Type\*:  Project  Subaward/Consortium

Organization: AMALGENT THERAPEUTICS, INC.

Start Date\*: 10-01-2025

End Date\*: 09-30-2026

Budget Period: 2

| <b>C. Equipment Description</b>  |                                   |
|--|-----------------------------------|
| List items and dollar amount for each item exceeding \$5,000               |                                   |
| Equipment Item   | Funds Requested (\$)*             |
| <b>Total funds requested for all equipment listed in the attached file</b> | <hr/>                             |
|  | <b>Total Equipment</b> <hr/> 0.00 |
| Additional Equipment: File Name:   |                                   |

| <b>D. Travel</b>   |  | <b>Funds Requested (\$)*</b> |
|--|--|------------------------------|
| 1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions) |  | 8,000.00                     |
| 2. Foreign Travel Costs  |  | <hr/>                        |
| <b>Total Travel Cost</b>   |  | <b>8,000.00</b>              |

| <b>E. Participant/Trainee Support Costs</b> |  | <b>Funds Requested (\$)*</b>                              |
|---|--|---|
| 1. Tuition/Fees/Health Insurance            |  |   |
| 2. Stipends                                 |  |   |
| 3. Travel                                   |  |   |
| 4. Subsistence                              |  |   |
| 5. Other:                                   |  |   |
| <b>Number of Participants/Trainees</b>      |  | <b>Total Participant Trainee Support Costs</b> <hr/> 0.00 |

RESEARCH &amp; RELATED Budget {C-E} (Funds Requested)

## RESEARCH &amp; RELATED BUDGET - SECTIONS F-K, Budget Period 2

UEI\*: CP5VN4N2MXX3

Budget Type\*:  Project  Subaward/Consortium

Organization: AMALGENT THERAPEUTICS, INC.

Start Date\*: 10-01-2025

End Date\*: 09-30-2026

Budget Period: 2

| F. Other Direct Costs                     |  | Funds Requested (\$)* |
|---|--|-----------------------|
| 1. Materials and Supplies                 |  | 5,000.00              |
| 2. Publication Costs                      |  |                       |
| 3. Consultant Services                    |  | 129,000.00            |
| 4. ADP/Computer Services                  |  |                       |
| 5. Subawards/Consortium/Contractual Costs |  | 1,200,000.00          |
| 6. Equipment or Facility Rental/User Fees |  |                       |
| 7. Alterations and Renovations            |  |                       |
| 8. Data Management and Sharing Costs      |  | 0.00                  |
| 9. Technical Assistance                   |  | 25,000.00             |
| Total Other Direct Costs                  |  | 1,359,000.00          |

| G. Direct Costs               |  | Funds Requested (\$)* |
|-------------------------------|--|-----------------------|
| Total Direct Costs (A thru F) |  | 1,496,600.00          |

| H. Indirect Costs    |  | Indirect Cost Type | Indirect Cost Rate (%) | Indirect Cost Base (\$) | Funds Requested (\$)* |
|----------------------|--|--------------------|------------------------|-------------------------|-----------------------|
| 1 . MTDC             |  |                    | 25.0                   | 296,600.00              | 74,150.00             |
| Total Indirect Costs |  |                    |                        |                         | 74,150.00             |

**Cognizant Federal Agency**  
(Agency Name, POC Name, and POC Phone Number)

| I. Total Direct and Indirect Costs                    |  | Funds Requested (\$)* |
|---|--|-----------------------|
| Total Direct and Indirect Institutional Costs (G + H) |  | 1,570,750.00          |

| J. Fee |  | Funds Requested (\$)* |
|--------|--|-----------------------|
|        |  | 108,203.00            |

| K. Total Costs and Fee |  | Funds Requested (\$)* |
|------------------------|--|-----------------------|
|                        |  | 1,678,953.00          |

|                          |   |
|--------------------------|---|
| L. Budget Justification* | File Name:<br>BudJust_merged_AT_FT_2024.09.03v2.pdf |
|--------------------------|---|

RESEARCH &amp; RELATED Budget {F-K} (Funds Requested)

## RESEARCH &amp; RELATED BUDGET - SECTION A &amp; B, Budget Period 3

UEI\*: CP5VN4N2MXX3

Budget Type\*:  Project  Subaward/Consortium

Enter name of Organization: AMALGENT THERAPEUTICS, INC.

Start Date\*: 10-01-2026

End Date\*: 03-31-2027

Budget Period: 3

| A. Senior/Key Person |             |             |            |        |               |             |          |          |        |              |                |                       |
|----------------------|-------------|-------------|------------|--------|---------------|-------------|----------|----------|--------|--------------|----------------|-----------------------|
| Prefix               | First Name* | Middle Name | Last Name* | Suffix | Project Role* | Base        | Calendar | Academic | Summer | Requested    | Fringe         | Funds Requested (\$)* |
|                      |             |             |            |        |               | Salary (\$) | Months   | Months   | Months | Salary (\$)* | Benefits (\$)* |                       |
| 1.                   | Malcolm     | A.          | Meyn       |        | PD/PI         | 180,000.00  | 3.0      |          |        | 45,000.00    | 9,000.00       | 54,000.00             |
| 2.                   | Sam         | C.          | Tetlow     |        | Co-I          | 180,000.00  | 0.6      |          |        | 9,000.00     | 1,800.00       | 10,800.00             |

**Total Funds Requested for all Senior Key Persons in the attached file**

|                                |            |                         |           |
|--------------------------------|------------|-------------------------|-----------|
| Additional Senior Key Persons: | File Name: | Total Senior/Key Person | 64,800.00 |
|--------------------------------|------------|-------------------------|-----------|

## B. Other Personnel

| Number of Personnel*     | Project Role*                       | Calendar Months | Academic Months | Summer Months | Requested Salary (\$)*                               | Fringe Benefits* | Funds Requested (\$)* |
|--------------------------|-------------------------------------|-----------------|-----------------|---------------|--|------------------|-----------------------|
| Post Doctoral Associates |                                     |                 |                 |               |  |                  |                       |
| Graduate Students        |                                     |                 |                 |               |  |                  |                       |
| Undergraduate Students   |                                     |                 |                 |               |  |                  |                       |
| Secretarial/Clerical     |                                     |                 |                 |               |  |                  |                       |
| <b>0</b>                 | <b>Total Number Other Personnel</b> |                 |                 |               | <b>Total Other Personnel</b>                         |                  | <b>0.00</b>           |
|                          |                                     |                 |                 |               | <b>Total Salary, Wages and Fringe Benefits (A+B)</b> |                  | <b>64,800.00</b>      |

RESEARCH &amp; RELATED Budget {A-B} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 3**

UEI\*: CP5VN4N2MXX3

Budget Type\*:  Project  Subaward/Consortium

Organization: AMALGENT THERAPEUTICS, INC.

Start Date\*: 10-01-2026

End Date\*: 03-31-2027

Budget Period: 3

| <b>C. Equipment Description</b>  |                                   |
|--|-----------------------------------|
| List items and dollar amount for each item exceeding \$5,000               |                                   |
| Equipment Item   | Funds Requested (\$)*             |
| <b>Total funds requested for all equipment listed in the attached file</b> | <hr/>                             |
|  | <b>Total Equipment</b> <hr/> 0.00 |
| Additional Equipment: File Name:   |                                   |

| <b>D. Travel</b>   |   | <b>Funds Requested (\$)*</b> |
|--|---|------------------------------|
| 1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions) |   | 8,000.00                     |
| 2. Foreign Travel Costs  |   | <hr/>                        |
|  | <b>Total Travel Cost</b> <hr/> 8,000.00 |                              |

| <b>E. Participant/Trainee Support Costs</b> |  | <b>Funds Requested (\$)*</b>                              |
|---|--|---|
| 1. Tuition/Fees/Health Insurance            |  |   |
| 2. Stipends                                 |  |   |
| 3. Travel                                   |  |   |
| 4. Subsistence                              |  |   |
| 5. Other:                                   |  |   |
| <b>Number of Participants/Trainees</b>      |  | <b>Total Participant Trainee Support Costs</b> <hr/> 0.00 |

RESEARCH &amp; RELATED Budget {C-E} (Funds Requested)

## RESEARCH &amp; RELATED BUDGET - SECTIONS F-K, Budget Period 3

UEI\*: CP5VN4N2MXX3

Budget Type\*:  Project  Subaward/Consortium

Organization: AMALGENT THERAPEUTICS, INC.

Start Date\*: 10-01-2026

End Date\*: 03-31-2027

Budget Period: 3

| F. Other Direct Costs                     |  | Funds Requested (\$)* |
|---|--|-----------------------|
| 1. Materials and Supplies                 |  |                       |
| 2. Publication Costs                      |  |                       |
| 3. Consultant Services                    |  | 45,000.00             |
| 4. ADP/Computer Services                  |  |                       |
| 5. Subawards/Consortium/Contractual Costs |  | 1,000,000.00          |
| 6. Equipment or Facility Rental/User Fees |  |                       |
| 7. Alterations and Renovations            |  |                       |
| 8. Data Management and Sharing Costs      |  | 0.00                  |
| 9. Technical Assistance                   |  | 25,000.00             |
| Total Other Direct Costs                  |  | 1,070,000.00          |

| G. Direct Costs               |  | Funds Requested (\$)* |
|-------------------------------|--|-----------------------|
| Total Direct Costs (A thru F) |  | 1,142,800.00          |

| H. Indirect Costs   |  | Indirect Cost Type | Indirect Cost Rate (%) | Indirect Cost Base (\$) | Funds Requested (\$)* |
|---|--|--------------------|------------------------|-------------------------|-----------------------|
| 1 . MTDC  |  |                    | 25.0                   | 117,800.00              | 29,450.00             |
| Total Indirect Costs  |  |                    |                        |                         | 29,450.00             |
| Cognizant Federal Agency<br>(Agency Name, POC Name, and POC Phone Number) |  |                    |                        |                         |                       |

| I. Total Direct and Indirect Costs                    |  | Funds Requested (\$)* |
|---|--|-----------------------|
| Total Direct and Indirect Institutional Costs (G + H) |  | 1,172,250.00          |

| J. Fee |  | Funds Requested (\$)* |
|--------|--|-----------------------|
|        |  | 80,308.00             |

| K. Total Costs and Fee |  | Funds Requested (\$)* |
|------------------------|--|-----------------------|
|                        |  | 1,252,558.00          |

|                          |   |
|--------------------------|---|
| L. Budget Justification* | File Name:<br>BudJust_merged_AT_FT_2024.09.03v2.pdf |
|--------------------------|---|

RESEARCH &amp; RELATED Budget {F-K} (Funds Requested)

## **BUDGET JUSTIFICATION**

This document justifies the budget for this project and provides a basis for the inclusion of the waiver topics published on May 21, 2024, entitled "Health and Human Services (HHS) Approved SBIR/STTR titled Topics for Awards over Statutory Budget Limitations". As stipulated on page 20, the National Institute on Drug Abuse (NIDA) will consider " A. Area 1. Substance Use and Addiction Drug Discovery and Development for SUD and medical consequences of drug use - Preclinical and/or clinical drug development" for a budget waiver. Amalgent Therapeutics, Inc is addressing the opioid crisis by repurposing the FDA-approved pramipexole, a dopamine type 3 (D3) receptor agonist, to develop a first-in-class pain medication. Unlike current therapies, which either rely solely on high-dose opioids or non-opioid alternatives with limited efficacy, AMGT-0220 leverages the synergistic effects of pramipexole and low-dose morphine, a commonly used opioid, to provide effective relief for moderate to severe pain while significantly reducing the risk of OUD and opioid tolerance. This drug, therefore, has the potential to replace high-dose opioid monotherapy to reduce the incidence of OUD and its consequences. As such, we respectfully request a hard-cap budget waiver for this proposal.

### **A. KEY PERSONNEL (Phase I Y1: \$51,840; Phase II Y1: \$129,600; Phase II Y2: \$64,800)**

#### Malcolm Meyn, PhD, MSHS (Phase I Y1: 2.4 Cal. Mon.; Phase II Y1: 6 Cal. Mon.; Phase II Y2: 3 Cal. Mon.)

Dr. Meyn, Project Principal Investigator, is the Chief Scientific Officer of Amalgent Therapeutics, Inc. He has extensive drug development experience, including directing research and development projects in regulated and non-regulated environments. He has experience managing CROs and other vendor contracts and has contributed to multiple pre-IND and IND submissions. He also has training in managing biotechnology projects, regulatory strategy, and clinical trial design. As PI of this project, he will oversee all aspects of the project.

#### Sam Tetlow, MBA (Phase I Y1: 0.48 Cal. Mon.; Phase II Y1: 1.2 Cal. Mon.; Phase II Y2: 0.6 Cal. Mon.)

Mr. Tetlow, President of Amalgent Therapeutics, Inc., has more than 30 years of experience as a successful entrepreneur and investor in life sciences companies. He has a functional focus on product development, sales, finance and corporate development. He will oversee budgetary matters for the project as well as coordinate with potential investors and lead internal program strategy.

The fringe benefits for four Employees are 20% of the money requested in Phases I and II.

### **B. OTHER PERSONNEL N/A**

### **C. EQUIPMENT N/A**

### **D. TRAVEL (Phase I Y1: \$0; Phase II Y1: \$8,000; Phase II Y2: \$8,000)**

Funds are requested to partially support travel costs for Dr. Meyn and Dr. Klein to travel to the clinical site. Anything in excess of the requested amounts will be covered by Amalgent's private funds.

### **E. PARTICIPANT/TRAINEE SUPPORT COSTS N/A**

### **F. OTHER DIRECT COSTS**

#### Materials and Supplies (Phase I Y1: \$5,000; Phase II Y1: \$5,000; Phase II Y2: \$0)

The requested amount will cover pass-through and shipping costs related to the clinical product.

#### Vendor Costs/Fee for Service Costs No funds requested.

#### Consultant Services (Phase I Y1: \$55,500; Phase II Y1: \$129,000; Phase II Y2: \$45,000)

#### Timothy Wright, BS (Phase I Y1: \$5,000; Phase II Y1: \$0; Phase II Y2: \$0)

Mr. Wright will serve as a strategic advisor on this project to help bring AMGT-0220 towards commercialization.

#### Gerald Klein, MD (Phase I Y1: \$7,500; Phase II Y1: \$7,500; Phase II Y2: \$7,500)

Dr. Klein provides Chief Medical Officer services to Amalgent Therapeutics, Inc. He is an accomplished expert in pain therapeutic drug development, which expertise in clinical research, medical monitoring, and pharmacovigilance, contributing to the development and commercialization of pain therapies. In this capacity, he will contribute to this project.

**Charles Argoff, MD** (Phase I Y1: \$0; Phase II Y1: \$2,500; Phase II Y2: \$2,500)

Dr. Argoff is a professor of Neurology and the director of the Comprehensive Pain Program at Albany Medical Center. He is a key opinion leader in the domain of pain management and will advise on clinical strategy.

**Colleen Kelly, PhD** (Phase I Y1: \$0; Phase II Y1: \$5,000; Phase II Y2: \$5,000)

Dr. Kelly will provide biostatistical support for this project, including providing input into clinical trial design to ensure sufficient statistical power to achieve study objectives and analysis of the data generated in the clinical trial. See provided letter.

**Allucent** (Phase I Y1: \$43,000; Phase II Y1: \$114,000; Phase II Y2: \$30,000)

Allucent will provide regulatory affairs consulting services to Amalgent Therapeutics, Inc, related to the preparation of all the components of the IND package and its submission to the FDA, IND maintenance, and clinical study report preparation and publishing, and coordinate interactions between Amalgent and the FDA, and other regulatory-related activities. See provided quote. Quoted costs above the requested amount will be covered by Amalgent Therapeutics, Inc.

**Fee-for-Service Contracts** (Phase I Y1: \$226,900; Phase II Y1: \$1,200,000; Phase II Y2: \$1,000,000)

**Catalent Pharma Solutions, LLC** (Phase I Y1: \$226,900; Phase II Y1: \$150,000; Phase II Y2: \$0)

Catalent is a leading CDMO with over 75 years of experience with extensive expertise development sciences, delivery technologies, and multi-modality manufacturing. They will be responsible for manufacturing and clinical release analysis of the clinical batch of AMGT-0220 and stability testing (Quote provided). Quoted costs above the requested amount will be covered by Amalgent Therapeutics, Inc.

**PPD** (Phase I Y1: \$0; Phase II Y1: \$1,050,000; Phase II Y2: \$1,000,000)

PPD is a clinical research business of Thermo Fisher Scientific. Its Austin Clinical Research Unit (CRU) has supported more than 1600 clinical trials and projects for the U.S. government in the last 30 years and have more than 70 active projects active contracts with the NIH, BARDA, CDC, DoD, and numerous non-profits and academia partners. This subaward will cover the cost of the Phase I pharmacokinetics study described in Phase II of this SBIR Fast Track project as well as the bioanalytical analysis of study samples at PPD's GMP facility. See provided letter and quotes for the clinical trial and sample analysis. Quoted costs above the requested amount will be covered by Amalgent Therapeutics, Inc.

**Data Management and Sharing Costs** No funds are requested.

**Discretionary Technical Assistance** (Ph I - Y1: \$6,500; Ph II - Y1: \$25,000; Y2: \$25,000)

The scope will include business activities as directed by Amalgent Therapeutic, Inc and is expected to include market analysis (reviewing competitive technologies, market size), expert/end-user interviews for market validation, identification of potential commercialization partner contacts, IP landscape review, market entry launch strategy, preparation of technology marketing material (pitch deck, technology flyer), outreach to potential commercialization partners, deal terms and licensing advisory, and fundraising strategy development. This work will be done by Foresight Science and Technology (Letter with quoted fee provided). Amalgent believes that this service will help validating our market, identify and connect with potential partners, and prepare for commercialization of AMGT-0220. Pursuant to 84 FR 12794 published by the Small Business Administration, these funds are requested above and beyond the hard cap budget limits prescribed.

**G. INDIRECT COSTS**

An indirect cost rate of 25% has been applied to all direct costs minus the fee-for-service contract costs that exceed \$25,000. This amount is appropriate to cover the company's current projected indirect costs.

**H. FEE**

A fee of 7% is requested, which we believe demonstrates a reasonable profit margin for for-profit organizations performing research and development work.



**Solution for**

**Analytical Development and Validation, Formulation Development, CTM Manufacture, Release Testing, and Stability of Pramipexole/Morphine Combination Drug Product, Two strengths (Phase II)**

VERSION: DualActivePDQ1C4

*Prepared for*

Amalgent Therapeutics, Inc.  
Malcolm Meyn  
Chief Scientific Officer  
[Malcolm@amalgent.com](mailto:Malcolm@amalgent.com)

*Provided by*

Catalent Pharma Solutions, LLC  
Ivelisse Ruiz  
Account Executive, North America – Pharma Product Delivery  
[Ivelisse.RuizLugo@catalent.com](mailto:Ivelisse.RuizLugo@catalent.com)

Kristin Coward  
Client Services Specialist  
1240 Sugg Parkway, Greenville, NC 27834  
[Kristin.Coward@catalent.com](mailto:Kristin.Coward@catalent.com)

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## Executive Summary

Amalgent Therapeutics, Inc. ("Amalgent") has requested Catalent Greenville, Inc. ("Catalent") to provide analytical method development and validation, formulation development, CTM manufacture, release, and stability for Pramipexole/Morphine combination IR tablets, 3 strengths (Phase II). The scope of work and associated costs are outlined below. The order in which actual work is performed may not follow the framework of this document.

All costs listed in this service estimate assume that the drug substance (Morphine) requires potent handling procedures (IIIA). A potent surcharge for analytical and pharmaceutical services has been added to this quote, where applicable. If the API was to be re-categorized as non-potent prior to initiation of or during the project, Catalent would omit the surcharges for any of the activities not already performed.

### Version History

| Version          | Revision Summary   |
|------------------|--|
| DualActivePDQ1R1 | Original service estimate (submitted on 08/13/2021)  |
| DualActivePDQ1R2 | Updated formulation to immediate-release, added excipient compatibility, added CTM manufacture, release, and stability   |
| DualActivePDQ1R3 | Updated from a bilayer tablet formulation to a IR tablet formulation throughout<br>Added blend uniformity testing to section 4.d.<br>Updated to two CTM strengths (sections 6, 7, and 8)   |
| DualActivePDQ1C1 | Reduced the number of excipients in the EC study from 8 to 7 and updated 2-week testing to optional (section 3)  |
| DualActivePDQ1C2 | Updated Dissolution and Content Uniformity methods to a combined method for Pramipexole and Morphine throughout the quote.<br>Updated Morphine release to 2 lots (section 4)<br>Added new section for optional regulatory support (section 12)<br>Added new section for optional development stability (section 13)<br>Added new section for RLD testing (section 14) and stability (section 15) |
| DualActivePDQ1C3 | Updated RLD testing for pramipexole dissolution (section 14)   |
| DualActivePDQ1C4 | Increased specialty material funds (section 11)<br>Updated demo stability outline and changed from optional to real cost (section 13)<br>Updated AssayRS methods to a combined method for Pramipexole and Morphine throughout the quote.<br>Added extra accuracy levels to validations (section 2)   |

Change Order 4 updates cost associated with changes in scope detailed in the above table. Change Order 4 will replace the original quote in its entirety. The net **DECREASE** for this project due to Change Order 4 is **\$10,820**.



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**Cost Estimate****1. Drug Substance Analytical Development**

- a. Develop and validate a cleaning verification procedure for Pramipexole and Morphine drug substances. Cost assumes two separate procedures, one per active. \$26,000
  - b. Generation of analytical monograph for Pramipexole API (appearance and IR-ID) and document maintenance. \$1,500
  - c. Generation of analytical monograph for Morphine API (appearance and IR-ID) and document maintenance. \$1,500
  - d. EH&S evaluation of both Pramipexole and Morphine drug substances. \$3,000
- Estimated cost for drug substance analytical development** \$32,000

**2. Drug Product Analytical Development and Validation (Phase II)**

- a. Develop a Pramipexole - ID, Assay and Related Substances (HPLC) method. \$13,700
- b. Validate a Combined Pramipexole and Morphine - ID, Assay and Related Substances (HPLC) method suitable for phase II. Method validation will include specificity, accuracy (high and low levels - 3 levels), intermediate precision (n=6; 2 analysts), linearity (low and high level), LOQ/LOD (confirmed replicates), stability of solution (NMT 72 hours), and filter study using a bracketing approach (low combination and high combination dosages). \$51,500
- c. Develop a Morphine - ID, Assay and Related Substances (HPLC) method. \$13,700
- e. Develop a combined Pramipexole and Morphine - Dissolution Profile (immediate release) method. \$9,300
- f. Validate a combined Pramipexole and Morphine - Dissolution Profile (HPLC, up to 5 pull points) method for immediate release dosage forms suitable for phase II. Method validation will include specificity, accuracy (5 levels), intermediate precision (n=6; 2 analysts), linearity (high level), stability of solution (NMT 72 hours), and filter study using a bracketing approach (low combination and high combination dosages). \$31,100
- i. Develop a combined Pramipexole and Morphine - Content Uniformity method. \$9,300



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|  |                      |
|--|----------------------|
| j. Validate a combined Pramipexole and Morphine - Content Uniformity (HPLC) method suitable for phase II. Method validation will include specificity, accuracy (4 levels), method precision (n=10), linearity (high level), stability of solution (NMT 72 hours), and filter study using a bracketing approach (low combination and high combination dosages). | \$25,500             |
| m. Develop a Moisture (KF) method.   | \$2,300 <sup>1</sup> |
| n. Qualify a Moisture (KF) method suitable for phase II. Method qualification will include method precision (n=3 titrations), linearity, and accuracy (3 individual) using a bracketing approach (low combination and high combination dosages).   | \$7,700 <sup>1</sup> |
| o. Verify the Microbial Enumeration Test (USP methods) using a bracketing approach (low combination and high combination dosages).   | \$5,600 <sup>1</sup> |
| <p><sup>1</sup>Cost assumes a single method will be developed to include both active ingredients. Should two methods be developed, the additional cost would be covered under a change order to this estimate. All analytical testing costs below (validation, release testing, stability, etc.) will be updated accordingly.</p>                              |                      |
| p. Validation protocols, final reports, and analytical monographs/specs for drug product (Phase II)  | \$14,000             |
| <b>Estimated cost for analytical develop/validation (Change Order 3)</b>   | <b>\$226,700</b>     |
| <b>Estimated cost for analytical develop/validation (Change Order 4)</b>   | <b>\$183,700</b>     |
| <b>Net decrease due to Change Order 4</b>  | <b>\$43,000</b>      |

NOTE: The activities listed in section above are subject to partial billing based on milestones and amount of work completed. The most likely partial billing will involve billing half of a line item total at certain point of the project and the remaining half at the completion of that particular activity.

### 3. Excipient Compatibility Study

Store Pramipexole API (1) and Morphine API (1) separately, store combined APIs (1), store 1:1 mixtures of Pramipexole and Morphine combined API with excipients (8), and control excipients (8) at 40°C/75%RH (open) and 60°C/ambient (closed). Perform gradient HPLC assays at time zero (T0), 2, 4 and 8 weeks. The excipient control samples will be optional testing, except at time zero (T0). Should the total number of excipients to be examined be reduced, terminated, or increased at any point, the testing costs would be adjusted accordingly.

- a. Sample preparation, stability storage/set-up \$10,000
- b. Assay and Related Substances (HPLC) testing at storage, 2 weeks, 4 weeks and 8 weeks:



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| Storage Condition                              | T0              | 2wk               | 4wk             | 8wk             | Total                       |
|--|-----------------|-------------------|-----------------|-----------------|-----------------------------|
| 40°C/75%RH – API (3) and Mixtures (7)          | \$14,500        | (\$14,500)        | \$14,500        | \$14,500        | \$43,500                    |
| 40°C/75%RH – Control Excipients (7)            | \$3,700         | (\$3,700)         | (\$3,700)       | (\$3,700)       | \$3,700                     |
| 60°C/Ambient – API (3) and Mixtures (7)        |                 | (\$9,300)         | \$9,300         | \$9,300         | \$18,600                    |
| 60°C/Ambient – Optional Control Excipients (7) |                 | (\$3,700)         | (\$3,700)       | (\$3,700)       | (\$11,100)                  |
| <b>Total</b>                                   | <b>\$18,200</b> | <b>(\$31,200)</b> | <b>\$23,800</b> | <b>\$23,800</b> | <b>\$65,800<sup>1</sup></b> |

<sup>1</sup>Total does not include any costs incurred due to OOS/OOT investigations or optional testing of control excipients.

**Estimated cost for excipient compatibility study (Change Order 1)      \$65,800**

#### 4. Formulation Development

Amalgent Therapeutics has inquired with Catalent to develop an immediate release tablet that is comprised of two active pharmaceutical ingredients - Pramipexole and Morphine. Once prototypes have been developed and stability studies have been conducted, Amalgent will evaluate the final dosage form in clinical trials for the treatment of pain against existing therapy.

In the final dosage form one strength of Pramipexole will be combined with two strengths of Morphine in ascending fashion, to arrive at two combinations:

0.125 mg Pramipexole/7.5 mg Morphine  
0.125 mg Pramipexole/15 mg Morphine

Final prototype will be manufactured (at high and low potency) and placed on short term informal stability. Clinical trial materials shall be manufactured based on mutually agreed upon performance of the prototype.

a. Release testing for one lot of Pramipexole API (IR-ID and appearance only; includes C of A).      \$1,200

b. Release testing for two lots of Morphine API (IR-ID and appearance only; includes C of A).      \$2,400

<sup>1</sup>If more than one container or lot of API is supplied and tested, then additional charges will apply (\$1,200/container). If previously released API is used, then this cost will not be applied.

c. Catalent proposes to develop a tablet formulation for fixed dose combination demonstration batch of Pramipexole/Morphine IR tablets. Manufacturing process assumes granulation, blending, and



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compression. Cost includes in-process testing, and cleaning verification activities. \$154,200

- d. Analytical support testing for up to four (4) demonstration batches from section 4.c. Testing may include Blend Assay (HPLC, n=5 locations/batch), Assay and Related Substances (HPLC, single prep) and Dissolution IR (HPLC; n=6). Cost will vary depending on the actual testing performed. ~\$29,600
- e. Manufacture two (2) lead prototype (one low and one high potency) batches of fixed dose combination IR tablets using the formulation and process attributes established in 4.c. Manufacturing process assumes granulation, blending, and compression. Cost includes in-process physical testing, packaging for stability (bottles), and cleaning verification (1 campaign). \$91,100
- f. Analytical support testing for up to two (2) lead prototype batches from 4.e. Costs will be adjusted based on the actual testing performed. ~\$22,000

Blend Assay (HPLC, up to 5 locations/batch)  
 Appearance  
 ID (HPLC-RT)  
 ID (HPLC-UV)  
 Assay and Related Substances (HPLC, duplicate prep)  
 Dissolution Profile IR (HPLC, n=6, up to 6 pull pts.)  
 Water Content (KF)  
 Content Uniformity (HPLC, n=10)  
 Analytical Report

|  |                  |
|--|------------------|
| <b>Estimated cost for formulation development (Change Order 3)</b> | <b>\$310,100</b> |
| <b>Estimated cost for formulation development (Change Order 4)</b> | <b>\$300,500</b> |
| <b>Net decrease due to Change Order 4</b>                          | <b>\$9,600</b>   |

NOTE: The activities listed in section above are subject to partial billing based on milestones and amount of work completed. The most likely partial billing will involve billing half of a line item total at certain point of the project and the remaining half at the completion of that particular activity.

## 5. Prototype Batch Stability (Two Batches)

Store two lead prototype batches (one low and one high potency) at 25°C/60%RH and 40°C/75%RH. Packaging configuration: HDPE bottles with CRC cap.

| Storage Condition | Time (months)  |   |   |   |
|-------------------|----------------|---|---|---|
|                   | Initial        | 1 | 3 | 6 |
| 25°C/60%RH        | X <sup>1</sup> | X | X | X |
| 40°C/75%RH        |                | X | X | X |

<sup>1</sup>Analytical support testing results will be used for the initial time point.

Where X = Appearance, Assay and Related Substances (HPLC, single prep),  
Dissolution Profile IR (HPLC, n=6), and Moisture (KF)

### Stability storage and set up charges:

| Price Per Time Point | Number of Time Points | Number of Studies | Total          |
|----------------------|-----------------------|-------------------|----------------|
| \$300                | 6                     | 2                 | \$3,600        |
| Set-Up and Labeling  |                       |                   | \$1,400        |
| <b>Total</b>         |                       |                   | <b>\$5,000</b> |

## Stability testing:

| Storage Conditions | Time (Months)   |                 |                 |                             |
|--------------------|-----------------|-----------------|-----------------|-----------------------------|
|                    | 1               | 3               | 6               | Total                       |
| 25°C/60%RH         | \$9,000         | \$9,000         | \$9,000         | \$27,000                    |
| 40°C/75%RH         | \$3,740         | \$3,740         | \$3,740         | \$11,220                    |
| <b>Total</b>       | <b>\$12,740</b> | <b>\$12,740</b> | <b>\$12,740</b> | <b>\$38,220<sup>2</sup></b> |

<sup>2</sup>Total does not include any costs incurred due to OOS/OOT investigations, if applicable.

|   |          |
|---|----------|
| Estimated cost for prototype batch stability (Change Order 3) | \$57,260 |
| Estimated cost for prototype batch stability (Change Order 4) | \$43,220 |
| Net decrease due to Change Order 4                            | \$14,040 |

## 6. CTM Manufacture (Two Active Batches)

- a. Use charge for cGMP raw materials ~\$19,800<sup>1</sup>
  - b. Use charge for cGMP packaging components ~\$3,900<sup>1</sup>

<sup>2</sup>A \$3,300 use charge for each in-stock raw material and a \$1,300 use charge for each in-stock packaging component used in the CTM manufacturing process will be assessed. That is, if 6 raw materials are used in the process and the product is packaged in HDPE bottles, desiccant, and CR caps, the use charges would total \$23,700. Use charge covers purchase, USP/NF and EP testing, storage, inventory, dispensing, etc. Should Catalent be required to purchase an excipient or packaging component (i.e., an item



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not in stock), Catalent would invoice client for purchase and release instead of use charge.

|   |                       |
|---|-----------------------|
| c. Manufacture one cGMP batch of 0.125 mg Pramipexole/7.5 mg Morphine combination IR tablets, suitable for Phase II clinical trials (batch size: up to ~10,000 units). Manufacturing process assumes granulation, blending, and compression. Cost includes in-process physical testing. | \$62,600              |
| d. Manufacture one cGMP batch of 0.125 mg Pramipexole/15 mg Morphine combination IR tablets, suitable for Phase II clinical trials (batch size: up to ~10,000 units). Manufacturing process assumes granulation, blending, and compression. Cost includes in-process physical testing.  | \$62,600              |
| e. Cleaning verification (one campaign).  | \$25,000 <sup>2</sup> |
| <p><sup>2</sup>Cost is presented on a per campaign basis (\$25,000/campaign).</p>   |                       |
| f. Packaging/labeling (hand package) for two CTM batches (~300 bottles/batch); assumes 30 count HDPE bottles w/ CR caps and simple open labels.   | \$18,000              |
| <b>Estimated cost for CTM manufacture</b>   | <b>\$191,900</b>      |

Note: The costs above for CTM batch manufacture include generation of batch record in Catalent format, suitable for regulatory filing. If custom batch records are required by the client, additional hours utilized on batch record preparation and review will be billed to the client at an hourly rate of \$250.

#### **7. CTM Batch Release Testing (Two Active Batches)**

|  |                 |
|--|-----------------|
| a. Blend uniformity testing (two blend batches)                      | \$6,500         |
| Blend uniformity testing (HPLC, n=5 locations/batch)                 |                 |
| Analytical Report  |                 |
| b. Bulk release testing (two batches)                                | \$18,700        |
| Appearance   |                 |
| ID (HPLC-RT)   |                 |
| ID (HPLC-UV)   |                 |
| Assay and Related Substances (HPLC, duplicate prep)                  |                 |
| Dissolution IR (HPLC, n=6)   |                 |
| Content Uniformity (HPLC, n=10)                                      |                 |
| Moisture (KF)  |                 |
| MET  |                 |
| C of A   |                 |
| <b>Estimated cost for CTM batch release testing (Change Order 3)</b> | <b>\$35,300</b> |
| <b>Estimated cost for CTM batch release testing (Change Order 4)</b> | <b>\$25,200</b> |
| <b>Net decrease due to Change Order 4</b>                            | <b>\$10,100</b> |



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## 8. CTM Batch Stability (Two Active Batches)

Store two batches of Pramipexole/Morphine IR tablets (from section 6) at 25°C/60%RH, 30°C/65%RH and 40°C/75%RH. Packaging configuration: HDPE Bottles

| Storage Condition | Time (months)   |     |     |     |     |      |    |    |
|-------------------|-----------------|-----|-----|-----|-----|------|----|----|
|                   | Initial         | 1   | 3   | 6   | 9   | 12   | 18 | 24 |
| 25°C/60%RH        | XM <sup>1</sup> | X   | X   | X   | X   | XM   | X  | XM |
| 30°C/65%RH        |                 | (X) | (X) | (X) | (X) | (XM) |    |    |
| 40°C/75%RH        |                 | X   | X   | XM  |     |      |    |    |

<sup>1</sup>Release testing (section 7) will be used for the initial timepoint.

Where X = Appearance, Assay and Related Substances (HPLC, single prep), Dissolution IR (HPLC, n=6), and Moisture (KF)

M = MET

( ) = *Optional testing per client request*

Stability storage and set up charges:

|                     | Total           |
|---------------------|-----------------|
| Storage             | \$9,750         |
| Set-Up and Labeling | \$1,400         |
| <b>Total</b>        | <b>\$11,150</b> |

Stability testing:

| Storage Condition | Time (months)   |                 |                 |                |                 |                |                 | Total                       |
|-------------------|-----------------|-----------------|-----------------|----------------|-----------------|----------------|-----------------|-----------------------------|
|                   | 1               | 3               | 6               | 9              | 12              | 18             | 24              |                             |
| 25°C/60%RH        | \$9,000         | \$9,000         | \$9,000         | \$9,000        | \$11,080        | \$9,270        | \$11,410        | \$67,760                    |
| 30°C/65%RH        | (\$9,000)       | (\$9,000)       | (\$9,000)       | (\$9,000)      | (\$11,080)      |                |                 | (\$47,080)                  |
| 40°C/75%RH        | \$3,740         | \$3,740         | \$5,820         |                |                 |                |                 | \$13,300                    |
| <b>Total</b>      | <b>\$12,740</b> | <b>\$12,740</b> | <b>\$14,820</b> | <b>\$9,000</b> | <b>\$11,080</b> | <b>\$9,270</b> | <b>\$11,410</b> | <b>\$81,060<sup>2</sup></b> |

<sup>3</sup>Total does not include any costs incurred due to OOS/OOT investigations or optional testing if required.

|  |                  |
|--|------------------|
| <b>Estimated cost for CTM batch stability (Change Order 3)</b> | <b>\$121,030</b> |
| <b>Estimated cost for CTM batch stability (Change Order 4)</b> | <b>\$92,210</b>  |
| <b>Net decrease due to Change Order 4</b>                      | <b>\$28,820</b>  |

## 9. Project Management **\$25,000<sup>1</sup>**

Includes:

- Schedule and facilitate project team teleconferences at regular intervals. Also includes time involved with teleconferences from team members.
- Coordinate with Catalent's project team to execute project plan and communicate project progress to client.
- Client main point of contact.

<sup>1</sup>The Project Management activity will be invoiced on a monthly basis at the rate of \$5,000 per month until active project management is not required for this project. An estimated cost has been listed for approximately five months of active project management. A



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change order could be issued to cover additional duration of active project management if needed and/or added to subsequent new service estimates for this project.

**10. Storage, Dispensing, and Shipping (estimated cost)** ~\$10,000

A nominal charge will be made for storage, dispensing, and shipment of GMP materials. A monthly charge of \$800 will cover storage of API and drug product lots specific to this project in a GMP warehouse under controlled room temperature. This fee covers approximately two pallets of warehouse space used on an interim/temporary basis. Any storage need exceeding two pallets or specialized storage (i.e., cold storage, controlled substance, etc) is also not included and will be quoted separately if needed.

A charge of \$1,500 will be applied for each dispensing operation (for up to four lots) and \$250 per each additional lot (may include dispensing in cGMP area, inventory control, labeling, and room cleaning). Client will be invoiced for use of any in-stock packaging materials as per the costs listed below. Should client require packaging materials not in-stock, client will be invoiced for purchase of materials at cost plus 10%. All shipment costs will be charged to the client at cost plus 10%. If the client's courier account is used for the shipment, then the shipping charge will not apply.

All Non-GMP material will incur a charge of \$250 for each dispensing, standard packaging and standard domestic shipment (up to four lots and/or two cubic foot cardboard shipper). Additional charge will apply based on requirement if specialized packaging or shipping is requested.

| Packaging Material                                | Standard Cost |
|---|---------------|
| Standard Cardboard Box                            | No Charge     |
| Controlled Room Temperature Shipper (15°C - 25°C) | \$165         |
| Refrigerated Shipper (2°C - 8°C)                  | \$40          |
| TempTale Monitor                                  | \$35          |

**11. Specialty Materials (estimated cost)** ~\$45,000

Purchase of specialty materials to support the above activities. These items include, but are not limited to, reference materials, analytical columns, and specialty chemicals. An approximate cost is presented; however, the final charge

|  |                 |
|--|-----------------|
| <b>Estimated cost for development batch stability (Change Order 3)</b> | <b>\$15,000</b> |
| <b>Estimated cost for development batch stability (Change Order 4)</b> | <b>\$45,000</b> |
| <b>Net increase due to Change Order 4</b>                              | <b>\$30,000</b> |



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**12. Optional - Ad Hoc Regulatory Support** **\$6,300**

*Catalent's global regulatory affairs will conduct the following activities:*

- *Provide regulatory advice in relation to product development and associated regulatory filing strategy, as required.*
- *Regulatory advice may relate to current and future phases of development.*

| <b>Activity</b>                  | <b>Estimated Cost</b>           |
|----------------------------------|---------------------------------|
| <i>Ad Hoc Regulatory Support</i> | <i>\$6,300 (\$350 per hour)</i> |

*Notes and Assumptions:*

1. *Activities will be cumulatively charged on an hourly basis as activities are performed, up to eighteen (18) hours at a rate of \$350 per hour.*
2. *Additional required ad hoc support (over eighteen (18) hours) will be noted and jointly agreed upon in project correspondence with the Client. Should significant elements of work be identified, these will be subject to separate and agreed quotation amendment record(s) (QAR) before proceeding.*

**13. Development Batch Stability (Two Batches)**

- a. Store two development batches at 25°C/60%RH and 40°C/75%RH. Packaging configuration: HDPE bottles with CRC cap.

| Storage Condition | Time (months)  |   |   |   |
|-------------------|----------------|---|---|---|
|                   | Initial        | 1 | 3 | 6 |
| 25°C/60%RH        | X <sup>1</sup> | X | X | X |
| 40°C/75%RH        |                | X | X | X |

<sup>1</sup>Analytical support testing results will be used for the initial time point.

Where X = Appearance, Assay and Related Substances (HPLC, single prep),  
Dissolution Profile IR (HPLC, n=6), and Moisture (KF)

Stability storage and set up charges:

| Price Per Time Point | Number of Time Points | Number of Studies | Total          |
|----------------------|-----------------------|-------------------|----------------|
| \$300                | 6                     | 2                 | \$3,600        |
| Set-Up and Labeling  |                       |                   | \$1,400        |
| <b>Total</b>         |                       |                   | <b>\$5,000</b> |

Stability testing:

| Storage Conditions | Time (months)   |                 |                 |                             |
|--------------------|-----------------|-----------------|-----------------|-----------------------------|
|                    | 1               | 3               | 6               | Total                       |
| 25°C/60%RH         | \$12,640        | \$12,640        | \$12,640        | \$37,920                    |
| 40°C/75%RH         | \$4,780         | \$4,780         | \$4,780         | \$14,340                    |
| <b>Total</b>       | <b>\$17,420</b> | <b>\$17,420</b> | <b>\$17,420</b> | <b>\$52,260<sup>2</sup></b> |



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<sup>2</sup>Total does not include any costs incurred due to OOS/OOT investigations, if applicable.

- b. Store one development batch at 40°C/75%RH open bottle, 60°C closed bottle without desiccant, and 60°C closed bottle with desiccant. Store a control of 1:1 morphine:pramipexole stored at 60°C closed bottle without desiccant.

| Storage Condition           | Time (months)  |   |
|-----------------------------|----------------|---|
|                             | Initial        | 3 |
| 40°C/75%RH open             | X <sup>1</sup> | X |
| 60°C closed w/out desiccant |                | X |
| 60°C closed w/ desiccant    |                | X |

<sup>1</sup>Analytical support testing results will be used for the initial time point.

Where X = Assay and Related Substances (HPLC, single prep)

Stability storage and set up charges:

| Price Per Time Point | Number of Time Points | Number of Studies | Total          |
|----------------------|-----------------------|-------------------|----------------|
| \$300                | 3                     | 1                 | \$900          |
| Set-Up and Labeling  |                       |                   | \$1,400        |
| <b>Total</b>         |                       |                   | <b>\$2,300</b> |

Stability testing:

| Storage Conditions          | Time (months)              |
|-----------------------------|----------------------------|
|                             | 3                          |
| 40°C/75%RH open             | \$3,620                    |
| 60°C closed w/out desiccant | \$1,040                    |
| 60°C closed w/ desiccant    | \$520                      |
| <b>Total</b>                | <b>\$5,180<sup>2</sup></b> |

<sup>2</sup>Total does not include any costs incurred due to OOS/OOT investigations, if applicable.

|   |                 |
|---|-----------------|
| <b>Estimated cost for development stability (Change Order 3 - Optional)</b> | <b>\$57,260</b> |
| <b>Estimated cost for development stability (Change Order 4)</b>            | <b>\$64,740</b> |
| <b>Net increase due to Change Order 4</b>                                   | <b>\$64,740</b> |

#### 14. RLD Sourcing and Analytical Testing

- a. Sourcing of Morphine RLD (~5 bottles) and Pramipexole RLD (~5 bottles). \$3,500
- b. Dissolution testing (HPLC, n=12, 4 medias) for Morphine RLD. Cost includes analytical report. \$11,400
- c. Dissolution testing (HPLC, n=12, 4 medias) for Pramipexole RLD. Cost includes analytical report. \$11,400



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|   |                 |
|---|-----------------|
| <b>Estimated cost for RLD sourcing/testing (Change Order 3)</b> | <b>\$26,300</b> |
|---|-----------------|

**15. RLD Stability (Two Batches)**

Store two RLD batches at 25°C/60%RH and 40°C/75%RH. Packaging configuration: HDPE bottles with CRC cap.

| Storage Condition | Time (months) |     |     |    |
|-------------------|---------------|-----|-----|----|
|                   | Initial       | TBD | TBD | 12 |
| 25°C/60%RH        | X             | X   | X   | X  |
| 40°C/75%RH        |               | X   | X   | X  |

Where X = Appearance, Assay and Related Substances (HPLC, single prep),  
Dissolution Profile IR (HPLC, n=6), and Moisture (KF)

Stability storage and set up charges:

| Price Per Time Point | Number of Time Points | Number of Studies | Total          |
|----------------------|-----------------------|-------------------|----------------|
| \$300                | 6                     | 2                 | \$3,600        |
| Set-Up and Labeling  |                       |                   | \$1,400        |
| <b>Total</b>         |                       |                   | <b>\$5,000</b> |

*Optional Stability testing:*

| Storage Conditions | Time (months)   |                 |                 |                             |
|--------------------|-----------------|-----------------|-----------------|-----------------------------|
|                    | TBD             | TBD             | 12              | Total                       |
| 25°C/60%RH         | \$12,640        | \$12,640        | \$12,640        | \$37,920                    |
| 40°C/75%RH         | \$4,780         | \$4,780         | \$4,780         | \$14,340                    |
| <b>Total</b>       | <b>\$17,420</b> | <b>\$17,420</b> | <b>\$17,420</b> | <b>\$52,260<sup>1</sup></b> |

<sup>1</sup>Total does not include any costs incurred due to OOS/OOT investigations, if applicable.

|  |                            |
|--|----------------------------|
| <b>Estimated cost for RLD stability (Change Order 2)</b> | <b>\$5,000<sup>1</sup></b> |
|--|----------------------------|

<sup>1</sup>Cost does not include optional testing listed above.

|  |                                |
|--|--------------------------------|
| <b>Estimated total cost for services detailed above (Change Order 3)</b> | <b>\$1,121,390<sup>1</sup></b> |
| <b>Estimated total cost for services detailed above (Change Order 4)</b> | <b>\$1,110,570<sup>1</sup></b> |
| <b>Net decrease due to Change Order 4</b>                                | <b>\$10,820</b>                |

<sup>1</sup>Total cost does not include optional testing listed above.

|                        |                  |
|------------------------|------------------|
| <b>Project Deposit</b> | <b>\$160,000</b> |
|------------------------|------------------|

The project deposit will be invoiced upon signing of this contract or receipt of PO from the Customer. This deposit will be returned to the Customer as a credit towards invoices of the last major milestones of this project (\$80,000 from sections 4 and 6).

The project will start once the fully executed proposal and a purchase order are received by Catalent.



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This Quotation is valid for 60 days from the date hereof and becomes binding if signed and delivered by both parties during that period.

**16. Revisions to Pricing**

Catalent reserves the right to revise quoted costs for any project as a result of initial scope change, planned deviations, revisions in specifications, modifications of test methods, undocumented requirements, retesting, requirements outside of Catalent SOPs, or any unforeseen difficulty in executing the project. In addition, the quoted costs are subject to annual review to account for changes in inflation, increased overhead charges, etc. Any additional work will be performed based on written agreement from Client and will be documented on a Catalent Quotation Amendment Record (QAR).

**17. Invoicing Terms**

Catalent will issue invoices for milestones completed. Where a milestone may include multiple batches, each batch will be invoiced when completed along with the in-process release testing costs, etc. If a draft report is issued an invoice will be generated for the report and Client will have 10 business days to return comments to Catalent. Following the 10 day period, if comments are received after issuance of the final report, Client will be billed for the time required to complete changes and reissue the report.

**18. Payment Terms**

Payments for all invoices are due within thirty (30) days after the date of invoice and are non-refundable. Any applicable wire transfer fees must be included in the payment issued to Catalent. All shipments are EXW (Incoterms® 2020) Greenville, NC. Remit all payments to:

Physical U.S. Mail Remittance

Catalent Greenville, Inc.  
P.O. Box 734097  
Chicago, IL 60673-4097

Electronic Wire/ACH Instructions

J.P. Morgan Chase  
Routing No: 021000021  
Account No: 305619352  
Swift Code: CHASUS33 (for international payments only)



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## **Additional Project Terms**

### **19. Samples/Materials**

If available, Client will provide all samples/materials necessary to perform this project. The samples/materials should arrive at Catalent with all proper documentation. If samples/materials are not available, upon request from Client, Catalent will purchase all samples/materials necessary to perform the project. Where standard materials, such as excipients or columns are required, or needed to maintain the Project timeline, Catalent will purchase such materials. Catalent will invoice Client monthly at cost plus reasonable and customary acquisition and handling costs for any material purchased as described above. Non-standard or special instrumentation or equipment required solely for this project will be invoiced to Client following Client's approval. If necessary, Catalent may engage a third party laboratory to perform analytical services on API or other Client supplied samples/materials related to the project activities at no additional cost to Client.

### **20. Termination or Cancellation**

Either party may terminate the project or any portion thereof at any time by providing 30 days written notice. Upon receipt of any such notice of termination, Catalent will promptly scale down the affected portion of the project and avoid (or minimize, where non-cancelable) any further related expenses.

If this project is cancelled by Client for any reason within their control or terminated by the Client, Catalent will invoice Client the cost of any sample/materials, work performed before cancellation or termination date, reference materials, equipment and supplies purchased by Catalent specifically for the project.

For manufacture, Catalent reserves the right to invoice project cancellation or delay fees according to the following calendar day schedule: batch cancellation or delay notice of 20 to 29 days – 25% of cost for batch manufacture, 10 to 19 days – 50% of cost for batch manufacture, 4 to 9 days – 75% of cost for batch manufacture, and 0 to 3 days – 90% of cost for batch manufacture.

### **21. Project Notes and Assumptions**

Client shall pay for all product batches, including batches that do not conform to applicable specifications, unless all methods and processes associated with the manufacture, testing, and storage of that product have been fully validated in accordance with generally accepted standards of the pharmaceutical industry.

The costs associated with optional testing have not been included in the total estimated project cost.



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**Project Approval and Authorization**

***Amalgent Therapeutics, Inc.***

Malcolm A. Meyn III

Malcolm A. Meyn III (Jul 7, 2024 17:02 EDT)

Signature

***Catalent Greenville, Inc.***

Signature

**Malcolm A. Meyn III**

Printed Name

Printed Name

**Chief Scientific Officer**

Title

Title

**07-Jul-2024**

Date

Date

PO Number

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### **Catalent Pharma Terms and Conditions**

These Catalent Standard Terms and Conditions ("Terms and Conditions") govern and constitute a part of the quotation to which they are attached (collectively, this "Quotation"). Catalent shall have the right to cause any of its Affiliates to perform any of its obligations hereunder; *provided* that Catalent shall remain liable for the performance of such Affiliates.

#### **1. Definitions.**

**"Affiliate(s)"** means with respect to any Person, any other Person that directly, or indirectly through one or more intermediaries, controls, is controlled by, or is under common control with such Person. For the purposes of this definition, "**Person**" means an individual, a corporation, a limited liability company, a partnership, an association, a trust, or other type of entity or organization, including a government or a political subdivision or an agency thereof; and "**control**" (including, with correlative meanings, "controlled by" and "under common control with") shall mean possession, directly or indirectly, of the power to direct the management and policies of a Person, whether through the ownership of 50% or more of the voting interests of such Person, through contract, or otherwise.

**"API"** means the active pharmaceutical ingredient (whether chemical or biologic in nature) identified in this Quotation and used in the performance of the Project.

**"Applicable Laws"** means, with respect to Client, all laws, ordinances, rules, and regulations, currently in effect or enacted or promulgated during the term of this Quotation, and as amended from time to time, of each jurisdiction in which Client-supplied Materials and Product is or is intended to be produced, marketed, distributed, used, or sold; and with respect to Catalent, all laws, ordinances, rules, and regulations, currently in effect or enacted or promulgated during the term of this Quotation, and as amended from time to time, of the jurisdiction in which Catalent performs the Project; *provided* that cGMP shall not constitute Applicable Laws except to the extent expressly stated in this Quotation.

**"Client-supplied Materials"** means any material to be supplied by or on behalf of Client or from a vendor selected by Client to Catalent for use in the Project, including API, trial materials, Product, reference materials, or any Comparator Drug supplied or procured by or on behalf of Client.

**"Comparator Drug"** means an investigational or marketed pharmaceutical product (other than Product) or placebo used as a reference in a clinical trial of Product.

**"Product"** means a pharmaceutical product containing the API, as identified in this Quotation, which is a subject of this Project.

**"Project"** means the services performed by Catalent for Client under this Quotation.

**"Representatives"** of an entity means such entity's respective officers, directors, employees, agents, members, accountants, attorneys, consultants, or other professional advisors.

**2. Changes.** Any revision to this Quotation shall be set forth in a Quotation Amendment Record ("QAR") signed by both parties. A QAR may include revised or additional fees if (a) Client's requirements or any Client-provided information is inaccurate or incomplete, (b) the QAR revises Catalent's responsibilities, the Project specifications, protocols, applicable test methods, final review of test methods, procedures, instructions, assumptions, processes, test protocols, analytical requirements, or the timing of the Project, (c) Client requests an alternate report format and/or requests revisions to laboratory reports, (d) Client requests copies of laboratory data and other technical records relating to the Project (excluding a single copy of batch records, which will be provided for each batch manufactured hereunder), (e) this Quotation states other reasons for such fees, or (f) any unforeseen circumstances affects completion of the Project. The prices provided in this Quotation are subject to annual review to address changes in inflation, increased overhead charges, and other commercially reasonable factors.

**3. Client Responsibilities.** Client grants Catalent full authority to use any Client-supplied Materials for purposes of the Project. Unless otherwise agreed to by the parties in writing, Client at its cost and expense shall (a) provide complete and accurate scientific data regarding the Project, (b) deliver to Catalent all Client-supplied Materials and Product in quantities and quality sufficient to meet the requirements of the Project, within timelines consistent with the Project, and provide safety data sheets or other required documentation prior to delivery of Client-supplied Materials and Product, (c) review and approve all protocols and specifications for Project and Product, (d) if applicable, review and approve all in-process and finished Product test results to ensure conformity of such results with the agreed Product specifications, regardless of which party is responsible for finished Product release, (e) perform such other obligations of Client set forth in this Quotation, and (f) prepare all submissions to

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regulatory authorities in connection with the Product. Client shall always retain title to Client-supplied Materials and shall bear the risk of loss thereof. If samples/materials are not available, Catalent will, upon request from Client, purchase all samples/materials necessary to perform the Project. Should Catalent need to purchase reference standards, excipients, columns, or product specific reagents, Catalent will purchase such materials as required or needed to maintain the Project timeline. Catalent will invoice Client monthly at cost plus reasonable and customary acquisition and handling costs for any material purchased as described in preceding sentence. Non-standard or special instrumentation or equipment required solely for this Project will be invoiced to Client following Client's approval.

**4. Delivery.** Catalent shall deliver all Product, Comparator Drug and other materials that are the subject of the Project EXW (Incoterms 2020) the Catalent facility ("Facility"). To the extent not already held by Client, title and risk of loss shall transfer to Client upon tender of delivery and/or upon transfer to storage. In the event Catalent arranges shipping or performs similar loading or logistics services under the Project for Client at Client's request, such services are performed by Catalent as a convenience to Client only and do not alter the rights and responsibilities set forth in this Article 4. Catalent shall not be responsible for Product, Comparator Drug or Client-supplied Materials in transit, including procuring any insurance and the cost thereof, any transport fee, or any risk associated with any transit or customs delay, storage, delivery, or handling.

**5. Invoices and Payments.** Catalent shall invoice Client, including for milestones completed, as set forth in this Quotation or QAR. Payment of each invoice is due 30 days following the date of the invoice. Payment for Comparator Drug is as set forth in the terms of the Comparator Drug procurement Quotation.

Client shall pay for all Product batches, including batches that do not conform to applicable specifications, unless all methods and processes associated with the manufacture, testing, and storage of that Product have been fully validated in accordance with generally accepted standards of the pharmaceutical industry. The costs associated with optional testing have not been included in the total estimated Project cost. If necessary, Catalent may engage a third-party laboratory to perform analytical services on API or other Client-supplied Materials/samples related to the Project activities at no additional cost to Client.

Notwithstanding anything to the contrary in this Quotation, if at any time any payment is not received by Catalent by its due date, then Catalent may, in addition to other remedies available at law or in equity, charge interest on the outstanding sum from the due date (both before and after any judgment) at 2% per month until paid in full (or, if less, the maximum amount permitted by the governing law of these Terms and Conditions) and/or Catalent may require full or partial payment in advance or require Client to post a letter of credit before performing any further services of the Project or making any further shipments of Product hereunder; in each case without releasing Client from its obligations under this Quotation. Failure to bill for interest due shall not be a waiver of Catalent's right to charge interest.

**6. Taxes.** All sales, use, gross receipts, compensating, value-added, or other taxes, duties, registrations, tariffs, customs fees, license fees, and other amounts assessed by any tax jurisdiction, U.S. Customs or foreign equivalent, or any other regulatory authority (excluding Catalent's net income and franchise taxes) ("Taxes"), on or for Client-supplied Materials, services under the Project, or Product, prior to or upon provision or sale to Catalent or Client, as the case may be, whether assessed on Catalent or Client, are the responsibility of Client, whether paid by Catalent or Client, and either Client shall reimburse Catalent for all such Taxes paid by Catalent or such sums will be added to invoices directed to Client. If any deduction or withholding in respect of Taxes or otherwise is required by law to be made from any of the sums payable hereunder, then Client shall be obliged to pay to Catalent such greater sum as will leave Catalent, after deduction or withholding as is required to be made, with the same amount as it would have been entitled to receive in the absence of any such requirement to make a deduction or withholding.

**7. Quality Agreement.** Prior to Catalent providing any Project services that are required to be performed in accordance with GMP, the parties shall negotiate in good faith and enter into a quality agreement (as amended from time to time, the "Quality Agreement"). If determined necessary by Catalent, the parties shall enter into separate Quality Agreements for each Facility. In the event of a conflict between this Quotation and the Quality Agreement with respect to quality-related activities, including compliance with GMP, the provisions of the Quality Agreement shall govern. In the event of a conflict between this Quotation and the Quality Agreement with respect to any other matter, including allocation of risk, liability, and financial responsibility, the provisions of this Quotation shall govern.

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**8. Regulatory Inspections.** Catalent will promptly notify Client of any regulatory authority inspections directly relating to the Project. Client shall reimburse Catalent for reasonable and documented costs associated with such regulatory inspections.

**9. Audits.** Client or its Representatives may conduct quality assurance Facility audits at the frequency established in the Quality Agreement. There shall be no cost to Client for audits conducted every other year. Additional audits will be invoiced by Catalent separately at the then-current rate for such audits, *unless* such audit is "for cause". Any request for an audit must be provided at least 60 days in advance of the requested audit date unless otherwise agreed mutually by the parties. Audits shall be designed to minimize disruption of operations at the Facility. Any participating Representatives shall comply with the Facility's rules and procedures applicable to visitors; and Client shall indemnify and hold harmless Catalent for any action, activity, or omission of or by any Representatives relating to failure to follow the Facility's rules and procedures while at the Facility.

**10. Virtual Inspections or Audits.** Inspections by regulatory authorities under Article 8 or Client Facility audits under Article 9 may be conducted by live and/or pre-recorded (as may be applicable) video and audio streaming sessions from a Facility using (a) integrated wearable "Smart Glasses" or other technologies employed by Catalent in order to facilitate remote site visits; and/or (b) a set of related applications and software (collectively, the "**Virtual Technology**") to facilitate telepresence between Facility personnel and regulatory authorities or Client ("**VPP Services**"). Catalent has the right to change, modify, add to, or discontinue any feature of the VPP Services at any time, with prior notification to Client. Catalent shall provide access to live video streaming sessions via a web portal URL. Users of the Virtual Technology shall be responsible for maintaining the confidentiality of passwords and for installing anti-virus software and related protections applicable to the Virtual Technology being employed. Client may not record, by any technology or other means, any of the live video streaming sessions, or other data, information, or activities made available via the VPP Services.

**11. Regulatory Compliance.** Catalent shall obtain and maintain all permits and licenses with respect to general Facility operations in the jurisdiction in which Catalent performs the Project. Client shall obtain and maintain all other regulatory authority approvals, authorizations, permits and certificates, including those relating to the import, export, use, distribution and sale of API, Product, and Client-supplied Materials. Client shall reimburse Catalent for any payment Catalent is required to make to any regulatory authority pursuant to Applicable Laws relating to Catalent's formulation, development, manufacturing, processing, filling, packaging, storing, or testing of Client's Product or Client-supplied Materials at the Facility. Catalent shall not be obliged to perform any services under the Project which would involve any countries that are targeted by comprehensive sanctions, restrictions, or embargoes administered by the United Nations, the European Union, the United Kingdom, or the United States of America. Client may identify Catalent (using the name and facility information provided by Catalent) in regulatory submissions and related regulatory correspondence including Client's clinical trial applications, new drug applications, abbreviated new drug applications or foreign equivalent thereof and other regulatory submissions as required, provided that Client will notify Catalent in writing prior to identifying Catalent in any new clinical trial applications, new drug applications or foreign equivalents thereof.

**12. Client Warranties.** Client warrants that (a) any scientific data provided by Client regarding the Project is complete and accurate, (b) all Client-supplied Materials shall have been produced and provided to Catalent in accordance with Applicable Laws, shall comply with all applicable specifications, and shall not be adulterated, misbranded, or mislabeled within the meaning of Applicable Laws, (c) all results, data, samples, Client-supplied Materials, Product and other materials and deliverables provided to Client by Catalent shall be held, used and disposed of by or on behalf of Client as set forth in this Quotation and in accordance with Applicable Laws, specifically, Client shall not permit the human consumption of any such items except to the extent authorized by applicable regulatory authorities, (d) it has filed the requisite regulatory filings (if any) with regulatory authorities for the Product that is the subject of this Quotation, and (e) no transactions or dealings under this Quotation shall be conducted with or for any person or entity that is designated as the target of any sanction, restriction, or embargo administered by the United Nations, the European Union, the United Kingdom, or the United States of America.

**13. Catalent Warranties.** Catalent warrants that (a) it will perform the Project in accordance with the written specifications and Project instructions expressly set forth or referenced in this Quotation, and (b) no transaction or dealing under this Quotation shall be conducted with or for any person or entity that is designated as the target of any sanction, restriction or embargo administered by the United Nations, the European Union, the United Kingdom, or the United States of America. THE WARRANTIES SET FORTH IN THIS ARTICLE ARE THE SOLE AND EXCLUSIVE WARRANTIES MADE BY CATALENT TO CLIENT, AND CATALENT MAKES NO OTHER REPRESENTATION, WARRANTY, OR GUARANTEE OF ANY

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KIND WHATSOEVER, INCLUDING ANY IMPLIED WARRANTY OF MERCHANTABILITY, NON-INFRINGEMENT OR FITNESS FOR A PARTICULAR PURPOSE.

**14. Confidentiality and Non-Use.** All information disclosed by a party in connection with this Quotation shall be confidential and proprietary information, regardless of the form in which it is furnished, including written, verbal, visual, electronic, or in any other media or manner, and information acquired by observation or otherwise during any visit to the other party's facility, including VPP Services ("Confidential Information"); unless such information (a) is or becomes generally available within the industry to which such information relates other than through a breach of this Quotation, (b) is already known by recipient at the time of disclosure as evidenced by recipient's written records, (c) becomes available to recipient on a non-confidential basis from a source that is entitled to disclose it on a non-confidential basis, or (d) was or is independently developed by or for recipient without reference to Confidential Information of discloser as evidenced by recipient's written records. Recipient will not use discloser's Confidential Information except in connection with the performance of its obligations under this Quotation, and will not disclose, without discloser's prior written consent, discloser's Confidential Information to any third party, except that recipient may disclose discloser's Confidential Information (i) to its employees or its Affiliates who need to know such Confidential Information to perform such party's obligations under this Quotation, or (ii) as required to be disclosed by Applicable Law, *provided* that the recipient shall give discloser, if legally permissible, as much prior notice of such legally required disclosure as is practicable under the circumstances. This undertaking shall survive for 5 years following the date of this Quotation, except with respect to trade secrets, for which the obligations of this Article will continue for so long as such information remains a trade secret under Applicable Law.

**15. Intellectual Property.**

(1) **Definitions.** For purposes hereof, (a) "**Client Background IP**" means all intellectual property and related embodiments owned by or licensed to Client as of the Effective Date hereof or developed or controlled by Client other than in connection with the Project, (b) "**Catalent Background IP**" means all intellectual property and related embodiments owned by or licensed to Catalent as of the Effective Date or developed or controlled by Catalent other than in connection with services under this Project, (c) "**New Invention**" means any intellectual property developed by either party or jointly by the parties in connection with the Project, (d) "**Client Inventions**" means any New Invention that relates exclusively to Client Background IP or Client's patented API, and e) "**Catalent Inventions**" means any New Invention, other than a Client Invention, that (i) relates exclusively to Catalent Background IP, or (ii) relates to (a) patented Catalent Background IP, or (b) developing, formulating, manufacturing, filling, processing, packaging, analyzing, or testing pharmaceutical products generally.

(2) **Ownership of Intellectual Property.** All Client Background IP and Client Inventions shall be owned solely by Client and no right therein is granted to Catalent under this Quotation, except solely to the extent necessary for use in performing the Project. All Catalent Background IP and Catalent Inventions shall be owned solely by Catalent and no right therein is granted to Client under this Quotation. All New Inventions other than Client Inventions and Catalent Inventions, if any, shall be owned jointly by Catalent and Client, except as set forth in 15(4). The parties shall cooperate to achieve the allocation of rights to New Inventions set forth herein. Each party shall be solely responsible for costs associated with the protection of its intellectual property.

(3) **Ownership of Data.** Except as set forth in Section 15.2, all data and information resulting from the conduct of services under the Project shall be the sole property of Client and shall be subject to Client's exclusive use, commercial or otherwise.

(4) **License of Catalent Background IP and Catalent Inventions.** Subject to the terms and conditions of this Quotation, in the event that Catalent incorporates any Catalent Background IP or Catalent Inventions into the Product formulation, for Project services not employing patented Catalent Background IP, Catalent hereby grants to Client a non-exclusive, royalty-free, fully paid-up, worldwide, perpetual, irrevocable, transferable license, with the right to grant sublicenses, under all such Catalent Background IP and Catalent Inventions that Catalent incorporates into such Product formulation, solely to the extent necessary for Client to develop, use, conduct clinical trials for, seek regulatory approval for, market, offer for sale, sell, import, export, or otherwise commercialize such Product, but not to make or have made the Product other than by Catalent. For the avoidance of doubt, no license is granted to any Catalent Background IP or Catalent Inventions used in the Project that is not incorporated into the Product formulation.

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**16. Indemnification.** Catalent shall indemnify, defend, and hold harmless Client, its Affiliates, and their respective directors, officers, employees, agents, managers, members, and shareholders, in their capacities as such (collectively, the "**Client Indemnitees**") from and against any and all claims, losses, demands, liabilities, damages, costs, and expenses (including reasonable attorneys' fees and expenses and reasonable investigative costs) in connection with any suit, demand, or action by any third party (collectively, "**Loss**") in connection with, arising out of or resulting from (a) any breach of Catalent's representations, warranties, or covenants set forth in this Quotation or (b) any gross negligence or willful misconduct by Catalent; in each case except to the extent that any of the foregoing is in connection with, arises out of, or results from any Client Indemnitee's gross negligence, willful misconduct, or breach of this Quotation.

Client shall indemnify, defend, and hold harmless Catalent, its Affiliates, and their respective directors, officers, employees, agents, managers, members, and shareholders, in their capacities as such (collectively, the "**Catalent Indemnitees**") from and against any and all Loss in connection with, arising out of, or resulting from (a) any breach of Client's representations, warranties, or covenants set forth in this Quotation, (b) any manufacture, packaging, sale, promotion, distribution, or use of or exposure to Product or Client-supplied Materials, including product liability or strict liability, (c) Client's exercise of control over the Quotation to the extent that Client's instructions or directions violate Applicable Laws; (d) the conduct of any clinical trial utilizing any material or Product that is the subject of this Quotation, (e) any actual or alleged infringement or violation of any third-party patent, trade secret, copyright, trademark or other proprietary right by any Product, material, or information provided or specified by Client, including Client-supplied Materials, Confidential Information supplied by or on behalf of Client pursuant to this Quotation, or Product, or (f) any gross negligence or willful misconduct by Client; in each case except to the extent that any of the foregoing is in connection with, arises out of, or results from any Catalent Indemnitee's gross negligence, willful misconduct, or breach of this Quotation. In addition, with respect to Services related to a Product for which a Paragraph IV Certification has been submitted to the FDA, Client shall defend, indemnify and hold harmless the Catalent Indemnitees from and against any and all Loss in connection with, arising out of, or resulting from any federal regulatory filing by or on behalf of Client, any of Client's Affiliates, or any licensee of Client or its Affiliates, including Loss incurred by any Catalent Indemnitee arising from filings under 21 U.S.C. § 355 or Section 505 of the United States Food, Drug and Cosmetics Act (or non-U.S. equivalents) and any related suit, action, claim, or proceeding (including Loss associated with any Catalent Indemnitee's obligation to respond to any third-party subpoena).

**17. Limitations of Liability.** THE TOTAL LIABILITY OF CATALENT UNDER THIS QUOTATION OR ANY QAR SHALL IN NO EVENT EXCEED THE TOTAL FEES PAID BY CLIENT UNDER THIS QUOTATION OR ANY QAR.

CATALENT SHALL HAVE NO LIABILITY UNDER THIS QUOTATION OR ANY QAR FOR ANY AND ALL CLAIMS FOR LOST, DAMAGED, OR DESTROYED CLIENT-SUPPLIED MATERIALS, WHETHER OR NOT SUCH CLIENT-SUPPLIED MATERIALS ARE USED IN THE PROJECT OR INCORPORATED INTO PRODUCT.

NOTWITHSTANDING ANYTHING TO THE CONTRARY IN THE FOREGOING, ANY CALCULATION OF CATALENT'S LIABILITY SHALL EXCLUDE THE TOTAL FEES PAYABLE AND PAID BY CLIENT TO CATALENT FOR ALL DIRECT PASS-THROUGH COSTS (INCLUDING ANY COST OR EXPENSE FOR COMPARATOR DRUG ACQUIRED BY CATALENT OR ANY CATALENT AFFILIATE AS PART OF THE PROJECT).

NEITHER PARTY NOR ITS AFFILIATES SHALL BE LIABLE TO THE OTHER PARTY OR ITS AFFILIATES FOR (A) INDIRECT, INCIDENTAL, SPECIAL, PUNITIVE, OR CONSEQUENTIAL DAMAGES, (B) LOSS OF REVENUES OR PROFITS (WHETHER DIRECT OR INDIRECT), OR (C) LOSS OF DATA, IN EACH CASE ARISING OUT OF PERFORMANCE UNDER THIS QUOTATION OR ANY QAR, WHETHER IN CONTRACT, IN TORT, OR UNDER STATUTE, EVEN IF SUCH PARTY OR ANY OF ITS AFFILIATES HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGES.

**18. Insurance.** Each party shall, at its own cost and expense, obtain and maintain in full force and effect during the term of this Quotation the following: (a) commercial general liability and/or foreign liability insurance with a per-occurrence limit of not less than \$2,000,000 or equivalent and an annual aggregate limit of not less than \$4,000,000 or equivalent; (b) products and completed operations liability insurance with a per-occurrence limit of not less than \$10,000,000 or equivalent covering each party's own operations arising out of or connecting with this Quotation, providing coverage for bodily injury and property damage claims, and (c) employers liability insurance with limits of not less than \$1,000,000 per claim, and if applicable to the jurisdiction, workers' compensation insurance with statutory limits. Client shall, at its own cost and expense, obtain and maintain clinical trial liability insurance with a per-occurrence limit of not less than \$10,000,000, and all-risk property insurance,

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including transit coverage, in an amount equal to the full replacement value of its property while in, or in transit to or from, the Facility, and Client shall obtain a waiver of subrogation clause from its all-risk property insurance carrier(s) in favor of Catalent. Each required insurance policy shall be obtained from an insurance carrier with an A.M. Best rating of at least A-VII or equivalent. If any required policy of insurance is written on a claims-made basis, then such policy shall be maintained throughout the term of this Quotation and for a period of at least 3 years thereafter. Catalent shall be named as an additional insured within Client's products liability and clinical trials liability insurance policies; *provided* that such additional insured status will apply solely to the extent of Client's indemnity obligations under this Quotation. Upon the other party's written request, each party shall promptly furnish to the other party a certificate of insurance or other evidence of the required insurance.

**19. Termination or Cancellation.** Either party may terminate this Quotation immediately without further action (i) if the other party files a petition in bankruptcy, enters into an agreement with its creditors, applies for or consents to the appointment of a receiver, administrative receiver, trustee or administrator for its affairs, makes an assignment for the benefit of creditors, suffers or permits the entry of any order adjudicating it to be bankrupt or insolvent where such order is not discharged within 30 days, or takes any equivalent or similar action in consequence of debt in any jurisdiction; or (ii) in the event of a material breach of any of the provisions of this Quotation (other than a payment breach), the non-breaching party shall have the right to terminate this Quotation but may only do so where the breaching party fails to cure the breach within 60 days after written notice of the breach is given by the non-breaching party. If Client fails to make payments in accordance with the terms of this Quotation and such payment breach is not cured within 10 days after written notice of non-payment from Catalent, Catalent may (i) terminate this Quotation or (ii) suspend any further performance of the Project under this Quotation until such invoice is paid in full, without releasing Client from its obligations under this Quotation. In addition to any other remedy that it may have under this Quotation or Applicable Law, either party may terminate this Quotation immediately and without notice if the other party breaches any of its warranties or covenants outlined herein. Catalent will invoice Client the cost of any Raw Materials, samples/materials prepared and ordered (non-cancellable) for the Project, and services performed before cancellation or termination date, and all reference materials, equipment and supplies purchased by Catalent specifically for the Project. For cancellation or postponement of any portion of this Quotation, Catalent will invoice Client a cancellation or postponement fee according to the following calendar-day schedule: <4 days = 100% of total Project cost; 4 – 9 days = 75% of total Project cost; 10 – 19 days = 50% of total Project cost; and 20 – 29 days = 25% of total Project cost.

**20. Amendment and Precedence.** These Terms and Conditions supersede any conflicting term set forth in this Quotation, QAR, purchase order, acknowledgement, delivery document, or the Specifications, and constitute the entire understanding between the parties concerning the Project, and supersede any contract, agreement, or understanding (oral or written) of the parties with respect to the Project. No provision of these Terms and Conditions may be amended except upon written agreement signed by both parties. These Terms and Conditions shall not impair or affect the terms of any other development, license, manufacturing, or packaging agreement between Client and Catalent or their respective Affiliates.

**21. Governing Law and Dispute Resolution.** This Quotation, and all suits, actions, claims or proceedings (whether in contract, tort, or statute) that may be based upon, arise out of, or relate to this Quotation, or the negotiation, execution, or performance of this Quotation (including any suit, action, claim, or proceeding based upon, arising out of, or related to any representation or warranty made in or in connection with this Quotation or as an inducement to enter into this Quotation), shall be governed by, and enforced in accordance with, the internal laws of the State of Delaware, USA, without giving effect to any law, rule, or provision of the State of Delaware, or to any other conflict of law principle, that would cause the application of the laws, rules, or provisions of any jurisdiction other than the State of Delaware. The United Nations Convention on Contracts for the International Sale of Goods shall not apply to this Quotation.

Any dispute between the parties in connection with, arising out of, or relating to this Quotation, QAR, or Project, shall first be presented to the respective senior executives of the parties for consideration and resolution. If such executives cannot resolve such dispute within 90 days of the receipt by one party of a written notice of demand from the other, the parties shall seek resolution of this dispute through final and binding arbitration in the English language, in New York, New York, USA, before one arbitrator and in accordance with the then-existing commercial arbitration rules of the CPR Institute for Conflict and Resolution, New York, NY. Notwithstanding anything to the contrary in this Quotation, the parties agree that final and binding arbitration shall be the mechanism by which any irreconcilable disputes shall be

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resolved and decided, and in so doing waive all rights to all other dispute resolution processes or proceedings, including litigation and administrative proceedings.

**22. No Waiver.** Failure by either party to insist upon strict compliance with any term of this Quotation in any one or more instances will not be deemed to be a waiver of its rights to insist upon such strict compliance with respect to any subsequent non-compliance.

**23. Independent Contractor.** The relationship of the parties is that of independent contractors, and neither party will incur any debt or make any commitment for the other party. Nothing in this Quotation is intended to create or will be construed as creating between the parties the relationship of joint venturers, partners, employer/employee, or principal and agent.

**24. Successors and Assigns.** This Quotation will be binding upon and inure to the benefit of the parties and their successors and permitted assigns. Neither party may assign this Quotation or these Terms and Conditions, in whole or in part, without the prior written consent of the other party; except that either party may, subject to prior written notice to the other party, assign this Quotation in its entirety to an Affiliate or to a successor to substantially all of the business or assets of the assigning party or the assigning party's business unit responsible for performance under this Quotation.

**25. No Third-Party Beneficiaries.** This Quotation shall not confer any right or remedy upon any Person other than the parties and their respective successors and permitted assigns.

**26. Publicity.** Neither party will make any press release or other public disclosure regarding this Quotation or the transactions contemplated hereby without the other party's prior written consent, except as required (a) under Applicable Laws, (b) by any governmental agency, or (c) by the rules of any stock exchange on which the securities of the disclosing party are listed; in each case the party required to make the press release or public disclosure shall provide a copy of the proposed public disclosure with commercially reasonable time provided to obtain the consent of the other party as to the form, nature, and extent of the press release or public disclosure prior to issuing the press release or making the public disclosure. In addition, Client shall not use Catalent's name in a manner that could be construed as an endorsement of Client's Product, including any scientific conclusion as to safety or efficacy.

**27. Right to Dispose and Settle.** If Catalent requests in writing from Client direction with respect to disposal of any inventory of Product, Client-supplied Materials, equipment, samples, or other items belonging to Client, and is unable to obtain a response from Client within a reasonable period after making reasonable efforts to do so, Catalent may, in its sole discretion (a) dispose of all such items and (b) set-off the cost of such disposal and all amounts due to Catalent or any of its Affiliates from Client against any credit Client may hold with Catalent or any of its Affiliates.

**28. Force Majeure.** Except as to payments required under this Quotation, neither party shall be liable in damages for, nor shall this Quotation be terminable or cancelable by reason of, any delay or default in such party's performance if such default or delay is caused by events beyond such party's reasonable control, including acts of God, any action or failure to act of any government or agency thereof occurring after the date of this Quotation, terrorist events, armed hostilities, factory shutdowns, embargoes, wars, or insurrection, riots, civil commotion, labor disturbances, epidemic, destruction of production facilities or materials by earthquakes, fires, floods, or weather, or failure of or shortages due to suppliers, vendors, public utilities or common carriers; *provided* that the party seeking relief under this Article shall promptly notify the other party of such cause(s) beyond such party's reasonable control. If the cause(s) continue unabated for 180 days, then both parties shall meet to discuss and negotiate in good faith what modifications to this Quotation should result from such cause(s).

**29. Survival.** The rights and obligations of Client and Catalent in Articles 5 (Invoices and Payments), 6 (Taxes), 11 (Regulatory Compliance), 12 (Client Warranties), 13 (Catalent Warranties), 14 (Confidentiality and Non-Use), 15 (Intellectual Property and Limitations), 16 (Indemnification), 17 (Limitations of Liability), 18 (Insurance), 19 (Termination), 21 (Governing Law and Dispute Resolution), 25 (No Third-Party Beneficiaries), 26 (Publicity), 27 (Right to Dispose and Settle), and 29 (Survival) of these Terms and Conditions shall survive termination or expiration of this Quotation.

Catalent Pharma Ts and Cs 16Nov2023 (US Law)



## Abbreviated Consulting Agreement (“ACA”)

To Provide Regulatory and Drug Development Consulting Services For:



**Amalgent Therapeutics, Inc. (“Sponsor”)**  
300 E. First St.  
Greenville, North Carolina 27514  
United States of America

Prepared by:

**Allucent**  
Allucent (US) LLC (together with its Affiliates)  
2000 Centregreen Way  
Cary  
NC, 27513  
USA

**BD Contact:** Trevor Brill-Freund, Sr. Director, Business Development  
ACA Date: 03 June 2024  
Allucent Ref: 17133  
Version 01

Sponsor and Allucent, each hereinafter a “Party” and both collectively as the “Parties”.



## Abbreviated Consulting Agreement

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### Confidentiality

The information provided to Allucent that was used to prepare this ACA, as well as the contents of this ACA, are confidential, and subject to the terms of the Confidentiality Agreement (CDA) executed between the Parties on 02 April 2024.

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### 1 Allucent

#### 1.1 Helping Bring New Therapies to Light

Allucent is a world-premier consulting and full-service CRO with expertise in most therapeutic areas and complex strategic areas, globally. Allucent has an impressive regulatory track record having been instrumental in the development of more than 60 marketed drugs approved by the United States (U.S) Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in the past 15 years.

Allucent brings a powerful blend of capabilities focused upon supporting small and mid-sized biotechnology organizations, representing a majority of our Sponsor's, top-tier pharmaceutical organizations, and investigator groups with their innovative research. We offer end to end services including the following:

- Consulting: Regulatory Affairs, Clinical Strategy, Medical Writing (MW), Chemistry, Manufacturing and Controls (CMC), Nonclinical, Pharmaceutical Development, and GxP Quality Assurance (QA);
- Clinical Pharmacology: Pharmacokinetics (PK), Pharmacodynamics (PD), Toxicology (TK), Population PK (PopPK), Quantitative Systems Pharmacology (QSP), Physiologically Based PK (PBPK), and Modeling and Simulation across all phases of drug development;
- Clinical Study Operations: Project Management, Study Start-Up, Investigator Selection, Site Management, Medical Affairs, and Pharmacovigilance (PhV);
- Biometrics: Data Management, Biostatistics, and Biostatistical Consulting.

Allucent nurtures a high performance culture, whereby we provide continuous training and emphasize personal and organizational development and opportunities, anchored by a commitment of the highest quality with personalized customer service.

We consider effective, frequent, and open communication as key components for developing strategies that will not only meet your requirements and goals, but exceed them. We provide lean project management to accomplish operational excellence in terms of timelines, quality, and fees.

Allucent employs more than 1,200 dedicated professionals, with 27 offices and operations in more than 50 countries around the world.

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## 2 Scope of Work

Projects are assigned and scheduled upon execution of this ACA. As part of the project Kick-Off Meeting (KOM), timelines and deliverables will be discussed. The Allucent Project Manager is responsible for understanding your timelines and communicating with Sponsor and the project team regarding how any changes in scope may impact timelines and/or the budget. All work conducted under this ACA will undergo Quality Control (QC) review as per Allucent's Standard Operating Procedures (SOPs).

### 2.1 Regulatory Consulting Services

Allucent will provide regulatory and consulting services as further set forth in the detailed services budget. Services include: kick-Off meeting, US regulatory contact services, ad-hoc strategic consulting, Fast Track Designation (FTD) authoring, review, and submission preparation activities, and annual report authoring.

### 2.2 Investigational New Drug (IND) Application

Allucent will:

- author portions of the IND, modules include 1, 2 (regulatory, nonclinical, CMC), 3 (drug substance descriptions and drug product descriptions);
- review the following IND modules: 4 (nonclinical study reports and literature references), 5 (clinical study reports and literature references); and
- provide project management.

Full details are set forth in the detailed service budget in Section 3 below.

### 2.3 Protocol Synopsis and Clinical Study Report

Allucent will develop an ICH-GCP compliant protocol for the study based on the protocol synopsis and other project specific information provided by Sponsor. Additionally, Allucent will generate a CSR shell and compile appendices.

### 2.4 IND Publishing and Maintenance; CSR Publishing

Allucent will provide compilation, publishing, and submission to the Regulatory Agency in eCTD format. Allucent will prepare and maintain a submission planner/tracker, compile, perform a QC review of the bookmarks, hyperlinks, and overall submission build, and submit to the Regulatory Agency in eCTD format via the Electronic Submissions Gateway (ESG). Allucent will provide Sponsor with one (1) electronic copy of each final submission. Authoring can be provided under a separate work order.

### 2.5 Project Coordination and Communication

Coordinating and communicating across multiple platforms requires effort from Allucent personnel that is not captured in the scope of work, which focuses upon scientific contributions to deliverables only. As such, project coordination and communication will include, but will not be limited to: the day to day coordination of the project; data transfer; archiving project related documents; meeting facilitation; ad-hoc teleconferences and meetings; project specific e-mail; communication with Sponsor.

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### 3 Service Fees, Term, and Payment Conditions

The budget in this ACA is presented in USD, as per below.

Services will commence upon full execution of this ACA and terminate on 31 May 2025. The term may be amended by the mutual written agreement of both Parties.

#### 3.1 Consulting Service Fees

Service fees are based upon the effort required to perform all Services delegated by Sponsor to Allucent. A summary of the Service budget is listed below.

#### Budget Summary

| Service Area                      | Total Price USD |
|-----------------------------------|-----------------|
| Regulatory Development Consulting | 88,726          |
| IND, CTA                          | 162,980         |
| Protocol, CSR                     | 68,760          |
| IND Publishing                    | 24,080          |
| IND Maintenance                   | 7,018           |
| CSR Publishing                    | 10,725          |
| <b>Total Service Fees</b>         | <b>362,288</b>  |

\*Estimated fees.

#### Detailed Service Fees

##### Regulatory Development Consulting

| Task                                | Unit ID | # of Units | Unit Price USD | Total Price USD | Project Specifications   |
|-------------------------------------|---------|------------|----------------|-----------------|--|
| <b>Project Start-up</b>             |         |            |                |                 | <b>8,679</b>   |
| Project Start-up                    | T&M     | -          | -              | 8,679           | Allucent will organize one internal and one external kick-off meeting, to be attended by 6 Allucent attendee(s). Allucent will provide meeting minutes and an action log following the meeting. Allucent will also put a risk and document management process in place, which will be maintained under other budget line items throughout the project. |
| <b>Regulatory Services</b>          |         |            |                |                 | <b>47,800</b>  |
| Regulatory Contact / Agent Services | Month   | 12         | 1,900          | 22,800          | Allucent will act as the designed Regulatory Contact/US Agent for Amalgent for US regulatory activities, for 1 compound(s)/IND(s). Assumes 4 hours per month. Any hours over this amount will be charged on a time-and-materials basis at the rates set forth below in the rate card.  |
| Strategic Consulting                | T&M     | -          | -              | 25,000          | Allucent will provide ad hoc strategic consulting services as requested by Amalgent.   |
| <b>Fast Track Designation (FTD)</b> |         |            |                |                 | <b>28,776</b>  |

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| Task   | Unit ID | # of Units   | Unit Price USD | Total Price USD | Project Specifications   |
|--|---------|--------------|----------------|-----------------|--|
| Fast Track Designation Package                   | T&M     |              |                | 21,287          | Allucent will author, review, and prepare the submission of a request for Fast Track Designation (FTD). Allucent will prepare the request based on information provided by Amalgent and reference up to 10 articles from the medical literature. Allucent will provide the FTD to Amalgent for up to two rounds of review, and Amalgent will return one set of consolidated comments after each review. Should the FDA request additional information, the time will be captured under a different work order. Assumes up to 30 documents. |
| FTD: Scientific Oversight and project management | T&M     |              |                | 5,783           | Allucent will manage timelines, scope, action items, prepare status reports, maintain files for 1 month(s). Allucent will also conduct up to 1 internal meeting(s) with 4 attendee(s).   |
| FTD: Sponsor meetings                            | T&M     |              |                | 1,707           | Allucent will schedule 1-hour teleconferences with Amalgent as needed throughout the course of the project. Allucent will provide a meeting agenda and action items. Assumes no more than 4 Allucent attendee(s) and 1 meeting(s).   |
| <b>Miscellaneous</b>                             |         | <b>3,470</b> |                |                 |  |
| Annual Report                                    | T&M     |              |                | 3,470           | Allucent will author annual report. Allucent will provide the document draft to Amalgent for up to one round of review, and Amalgent will return one set of consolidated comments.   |

### IND, CTA

| Task         | Unit ID | Total Price USD | Project Specifications   |
|--------------|---------|-----------------|--|
| <b>IND</b>   |         | <b>162,980</b>  |  |
| IND Module 1 | T&M     | 4,909           | Allucent will author the Form FDA 1571 provide to Amalgent for one round of review prior to finalization. Allucent will finalize and provide to Amalgent for signature, and Amalgent will return to Allucent within agreed upon timelines. Allucent will author the Form FDA 3674 provide to Amalgent for one round of review prior to finalization. Allucent will finalize. Allucent will author the Cover Letter and provide to Amalgent for one round of review prior to finalization. Allucent will incorporate comments, finalize, and provide to Amalgent for signature. Amalgent will return to Allucent within agreed upon timelines for submission to FDA. Assumes document will be no more than 3 pages in length. Allucent will verify inclusion of transfer of obligations, 1572, environmental analysis. Amalgent will author the General Investigational Plan. Allucent will provide 1 set consolidated comments. Amalgent |

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| Task                                      | Unit ID | Total Price USD | Project Specifications  |
|---|---------|-----------------|---|
|   |         |                 | will incorporate comments and return to Allucent for eCTD formatting and finalization within agreed upon timelines. Assumes document will be no more than 10 pages in length.   |
| Investigator's Brochure                   | T&M     | 35,434          | Allucent will author the Investigator's Brochure. Allucent will provide the document draft to Amalgent for up to one round of review, and Amalgent will return one set of consolidated comments. Allucent will incorporate comments and is responsible for eCTD formatting and finalization within agreed upon timelines. Assumes document will be no more than 75 pages in length. |
| IND Module 2: Regulatory                  | T&M     | 1,420           | Allucent will author all sections. Allucent will provide the document draft to Amalgent for up to one round of review, and Amalgent will return one set of consolidated comments. Allucent will incorporate comments and perform eCTD formatting and finalization within agreed upon timelines. Each section will be no more than 20 pages.   |
| IND Module 2: Clinical                    | T&M     | 14,588          | Allucent will author all sections. Allucent will provide the document draft to Amalgent for up to one round of review, and Amalgent will return one set of consolidated comments. Allucent will incorporate comments and perform eCTD formatting and finalization within agreed upon timelines. Each section will be no more than 20 pages.   |
| IND Module 2: Nonclinical                 | T&M     | 38,640          | Allucent will author all sections. Allucent will provide the document draft to Amalgent for up to one round of review, and Amalgent will return one set of consolidated comments. Allucent will incorporate comments and perform eCTD formatting and finalization within agreed upon timelines. Each section will be no more than 20 pages.   |
| IND Module 2: CMC                         | T&M     | 5,580           | Allucent will author all sections. Allucent will provide the document draft to Amalgent for up to one round of review, and Amalgent will return one set of consolidated comments. Allucent will incorporate comments and perform eCTD formatting and finalization within agreed upon timelines. Each section will be no more than 20 pages.   |
| IND Module 3: Drug Substance Descriptions | T&M     | 16,574          | Allucent will author Module 3 documents. Allucent will provide the document draft to Amalgent for up to one round of review, and Amalgent will return one set of consolidated comments. Allucent will incorporate comments and perform eCTD formatting and finalization within agreed upon timelines.   |
| IND Module 3: Drug Product Descriptions   | T&M     | 17,524          | Allucent will author Module 3 documents. Allucent will provide the document draft to Amalgent for up to one round of review, and Amalgent will return one set of consolidated comments. Allucent will incorporate comments and perform eCTD formatting and finalization within agreed upon timelines.   |

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| Task  | Unit ID | Total Price USD | Project Specifications   |
|---|---------|-----------------|--|
| IND Module 4: Nonclinical Study Reports     | T&M     | 4,000           | Amalgent will provide final safety pharmacology, ADME, and toxicology study reports to Allucent in submission-ready format. An Allucent toxicologist will review the reports for completeness and compare the data to Sections 2.4 and 2.6. An Allucent Toxicologist will also assign the appropriate study tagging files for each report within the eCTD Table of Contents. Any documents not provided in submission ready format will be subject to document remediation fees. |
| IND Module 4: Literature References         | T&M     | 1,000           | Amalgent will provide up to 10 publications to Allucent in PDF format. Allucent will review publications against those referenced in the nonclinical documents and perform document remediation services as necessary to ensure submission-readiness according to FDA guidance. The actual number of units will be dependent upon the final number of publications provided.   |
| IND Module 5: Clinical Study Reports        | T&M     | 2,730           | Amalgent will provide reports to Allucent in PDF format. Allucent will review publications against those referenced in the clinical documents and perform document remediation services as necessary to ensure submission-readiness according to FDA guidance. The actual number of units will be dependent upon the final number of reports provided.   |
| IND Module 5: Literature References         | T&M     | 888             | Amalgent will provide up to 10 publications to Allucent in PDF format. Allucent will review publications against those referenced in the clinical documents and perform document remediation services as necessary to ensure submission-readiness according to FDA guidance. The actual number of units will be dependent upon the final number of publications provided.  |
| Scientific Oversight and Project Management | T&M     | 19,694          | Allucent will manage timelines, scope, action items, prepare status reports, maintain files. Assumes 3 month(s). The Allucent project team will meet to discuss project status. Assumes 3 meeting(s) that will be no longer than 1- hour and have no more than 5 attendee(s).  |

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### Protocol, CSR

| Task   | Unit ID  | # of Units | Unit Price USD | Total Price USD | Project Specifications  |
|--|----------|------------|----------------|-----------------|---|
| <b>Protocol Synopsis, Manuscripts, Other Reports</b> |          |            |                | <b>29,831</b>   |   |
| Full Protocol Development                            | Protocol | 1          | 29,831         | 29,831          | Allucent's Medical Writer will prepare an ICH-GCP compliant protocol for this study based on the protocol synopsis and other project specific information provided by Amalgent. The protocol will describe the background, rationale, objective(s), design, methodology, statistical considerations and organization of the study. The protocol will contain scientifically sound knowledge about the safety, efficacy, and specific therapeutic characteristics of the new investigational product(s). Allucent will cover medical, clinical, scientific, statistical, and regulatory input and support into its development and will hold two meetings with Amalgent to discuss progress (a default of two review rounds is considered). Submission to authoritative bodies or preparation of amendments will be handled under a separate budget. |
| <b>Clinical Study Report</b>                         |          |            |                | <b>38,929</b>   |   |
| CSR Writing  | Report   | 1          | 33,390         | 33,390          | Allucent will generate a CSR shell and two drafts of the CSR results for Amalgent's review.   |
| Compiling Appendices                                 | Report   | 1          | 5,539          | 5,539           | Subject data listings and other appendices, e.g., 16.1.1 (protocols and amendments), 16.1.2 (eCRF), etc., will remain separate from the final CSR. This proposal assumes that all cross-document linking from the final CSR to subject data listings will be completed during publishing.   |

### IND Publishing

| Task   | Unit ID  | # of Units | Unit Price USD | Total Price USD |
|--|----------|------------|----------------|-----------------|
| <b>eCTD &amp; CSR Publishing</b>                                     |          |            |                | <b>21,270</b>   |
| Submission of 1-15 pages   | Sequence | 2          | 1,000          | 2,000           |
| Submission of >200 pages   | Sequence | 1          | 2,500          | 2,500           |
| Page count >200  | Page     | 4,800      | 3.25           | 15,600          |
| Data Sets, Programs, and define files (non pdf files e.g., SAS, xpt) | File     | 5          | 10             | 50              |
| Submissions under 7,500 pages, CRFs, TLFs                            | Page     | 100        | 1              | 100             |
| Document remediation   | T&M      |            |                | 1,020           |
| <b>Submission Management</b>   |          |            |                | <b>2,810</b>    |

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| Task                                 | Unit ID | # of Units | Unit Price USD | Total Price USD |
|--------------------------------------|---------|------------|----------------|-----------------|
| Submission Planning, & Project Setup | Project | 3          | 720            | 2,160           |
| New eCTD file                        | File    | 20         | 32.50          | 650             |

### IND Maintenance

| Task                                 | Unit ID       | # of Units | Unit Price USD | Total Price USD |
|--------------------------------------|---------------|------------|----------------|-----------------|
| <b>eCTD &amp; CSR Publishing</b>     |               |            |                | <b>2,000</b>    |
| Submission of 16-74 pages            | Sequence      | 1          | 2,000          | 2,000           |
| <b>Submission Management</b>         |               |            |                | <b>5,018</b>    |
| Submission Planning, & Project Setup | Project       | 1          | 720            | 720             |
| New eCTD file                        | File          | 3          | 32.50          | 98              |
| System Maintenance                   | User per Year | 12         | 350            | 4,200           |

### CSR Publishing

| Task                                      | Unit ID  | # of Units | Unit Price USD | Total Price USD |
|---|----------|------------|----------------|-----------------|
| <b>eCTD &amp; CSR Publishing</b>          |          |            |                | <b>9,225</b>    |
| Submission of >200 pages                  | Sequence | 1          | 2,500          | 2,500           |
| Page count >200                           | Page     | 1,300      | 3.25           | 4,225           |
| Submissions under 7,500 pages, CRFs, TLFs | Page     | 2,500      | 1              | 2,500           |
| <b>Submission Management</b>              |          |            |                | <b>1,500</b>    |
| Submission Planning, & Project Setup      | Project  | 1          | 720            | 720             |
| New eCTD file                             | File     | 24         | 32.50          | 780             |
| <b>Total Service Fees</b>                 |          |            |                | <b>362,288</b>  |

**Time and Materials tasks:** Items marked as Time and Materials (T&M) in the above detailed service fees, will be invoiced on a Time and Materials (T&M) basis in which Allucent will invoice Sponsor monthly based upon actual hours performed as per the hourly rates specified in the Allucent rate card in Appendix A.

**Unit-based tasks:** Where activity includes a number of units, Allucent will invoice Sponsor the for units achieved. Any additional revisions and/or activities will be addressed in a Change Order (CO) or billed on an hourly basis as per the hourly rates specified in the Allucent rate card in Exhibit A, provided Allucent has obtained prior written approval from Sponsor which may be in the form of e-mail.

The budget is capped at \$362,288. Allucent shall not invoice more than the capped amount without the prior written approval of Sponsor, which may be in the form of e-mail.

### **Payment Schedule**

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- Upon signature, Allucent will invoice Sponsor twenty percent (20%) (**\$72,457**) of the total amount of this ACA which will be held and reconciled against the final invoice under this ACA;
- Sponsor will pay Allucent invoices within thirty (30) days of receipt of an Allucent invoice.

### Invoicing Details

All invoices under this ACA will be addressed to the below Sponsor contact and project reference details:

**Amalgent Therapeutics, Inc.**  
206 Pebble Springs Road  
Chapel Hill, North Carolina 27514  
United States of America

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**No PO required.**

### Remittance Information

Remittance information will be included on the applicable invoice. In the event of a change in banking information, Allucent will provide Sponsor with a formal notice of such change which will be sent the address listed above, with a copy sent via e-mail.

### 3.2 Notes to Budget

This ACA is available to Sponsor for **45 days** from the date of issuance. All payments for Allucent consulting service fees as well as any advances are not subject to withholding taxes or other applicable taxes. Fees indicated in this ACA are valid during 2024.

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### 4 Terms

| Sponsor Information   |                             | Allucent Information                   |                   |
|---|-----------------------------|--|-------------------|
| <b>Company</b>  | Amalgent Therapeutics, Inc. | <b>Company and Operating Affiliate</b> | Allucent (US) LLC |
| <b>Compound</b>   |                             | <b>Project Code</b>                    | 17133             |
| Details of Services   |                             |  |                   |
| Allucent and Sponsor have agreed to work collaboratively. Allucent will provide the following Services as described in this ACA: <ul style="list-style-type: none"> <li>Regulatory and Drug Development Consulting Services ("Project" and/or "Services")</li> </ul> Details of the Project specific Services, timelines, key assumptions, and cost overview for this ACA are described herein, including, but not limited to; ad-hoc consulting services on an as needed basis according to the hourly rates specified in the Allucent rate card in Appendix A.<br>For any specific deliverables identified and delivered during the course of the engagement, Allucent assumes use of Allucent's SOPs, templates, standard document preparation, and review processes for all activities.   |                             |  |                   |
| Payment and Additional Terms  |                             |  |                   |
| <b>Service Fees</b><br>These fees are based upon the effort required to perform all Services delegated by Sponsor to Allucent as outlined in this ACA. Allucent will invoice Sponsor in accordance with Section 3.1 of this ACA.  |                             |  |                   |
| <b>Estimated Pass-Through Expenses</b><br>Any pass-through expenses shall be pre-approved by Sponsor in an e-mail if not otherwise agreed to between the Parties in this ACA.   |                             |  |                   |
| This budget is quoted in USD and will be invoiced in USD  |                             |  |                   |
| Allucent reserves its rights to increase fees for its Services and our rates annually by four percent (4%), or market rates, whichever is greater.  |                             |  |                   |
| If Sponsor disputes the amount due on any invoice, then Sponsor must notify Allucent of such dispute before the payment due date and pay such amount as is undisputed by the payment due date. Both Parties shall act in good faith to promptly resolve such dispute, and upon resolution of the dispute, any amount remaining due shall be paid within fifteen (15) days after the resolution.   |                             |  |                   |
| <b>Indemnification</b><br>Each Party ("Indemnifying Party" or the "Indemnitor") shall indemnify, defend, and hold harmless the other Party ("Indemnified Party" or the "Indemnitee") from, and against any claims, suits, actions, demands, liabilities, expenses, and/or losses including reasonable legal expenses and attorneys' fees (collectively, the "Losses") brought by a third-party, if such Losses or potential Losses are on account of the indemnitor's gross negligence, illegal misconduct, willful misconduct, breach of confidentiality protection, patent infringement, copyright infringement, trademark infringement, title claim, or misappropriation claim. The Indemnitee shall provide prior written notice to the Indemnitor after receiving any such claim and shall permit the Indemnitor to assume defense of such claim and shall further cooperate with the Indemnitor at Indemnitor's cost. |                             |  |                   |

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Abbreviated Consulting Agreement | v1.0 | Effective: 08 May 2024

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## Abbreviated Consulting Agreement

 Amalgent Therapeutics  
Allucent Ref #: 00042625  
V1.0 Draft  
03 June 2024

### **Limitation of Liability**

To the extent permitted by applicable laws, neither Party shall be liable to the other Party under this ACA for any special, incidental, punitive, consequential, or other indirect, or exemplary damages arising in any way out of, or under this ACA, including, without limitation, lost profits, whether in tort, contract, or otherwise, even if such Party has been advised of the possibility of such damages. This section shall survive any expiration or other termination of this ACA.

### **Insurance**

During the term of this ACA, each Party shall maintain, at its sole expense, insurance on commercial general liability and Errors and Omission each of which is not less than **\$1,000,000 USD** in limit, both in per claim and in aggregate, and Workers Compensation maintained at the required statutory levels. Upon request, a Party shall provide the other with certificates of insurance evidencing coverage.

This ACA cancels and supersedes all other prior written or oral agreements, representations and understandings between the Parties, and further any changes or modification to this ACA will be effective only if agreed to between both the Parties in writing, such as a Change Order (CO) and/or Amendment, though not strictly limited to these, and further signed by the authorized representative of both Parties.

**Sponsor and Allucent have reviewed the specifications and fees described in this ACA and agree that Allucent shall provide, and Sponsor shall pay Allucent for such Services.**

*[Signatures on the following page]*

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➤ Abbreviated Consulting Agreement | v1.0 | Effective: 08 May 2024

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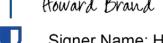
## Abbreviated Consulting Agreement

 Amalgent Therapeutics  
Allucent Ref #: 00042625  
V1.0 Draft  
03 June 2024

### 5 Signatures

In witness whereof, the Parties hereto have caused this ACA to be executed by their respective duly authorized representatives as of the Effective Date which is the last date of signature appearing in the signature block provided below.

Signed on behalf of and for:

|                             | Name and Title   | Date and Signature   |
|-----------------------------|--|--|
| <b>Allucent Approval by</b> | Howard Brand<br>VP, Finance                            | DocuSigned by:<br><br>Signer Name: Howard Brand<br>Signing Reason: I approve this document<br>Signing Time: 27-Jun-2024   14:24 PDT<br>87F9996B564A4D08A25AEA0996CC32F6    |
| <b>Sponsor Approval by</b>  | Malcolm A. Meyn, PhD, MSHS<br>Chief Scientific Officer | DocuSigned by:<br><br>Signer Name: Malcolm A. Meyn<br>Signing Reason: I approve this document<br>Signing Time: 26-Jun-2024   14:37 EDT<br>4EC522914E46464880F7DFF3C4FE4CE0 |

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Abbreviated Consulting Agreement | v1.0 | Effective: 08 May 2024

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## Abbreviated Consulting Agreement



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03 June 2024

### Appendix A – Allucent Rate Card

|   | NA*   | WEU   | EEU   | IND*  |
|---|-------|-------|-------|-------|
| Title   | 2024  | 2024  | 2024  | 2024  |
| Submissions                                   |       |       |       |       |
| Submissions Specialist                        | N/A   | € 130 | € 100 | \$75  |
| Submissions Publisher                         | N/A   | € 160 | € 120 | \$85  |
| Submissions Senior Publisher                  | N/A   | € 185 | € 145 | \$110 |
| Submissions Manager                           | \$315 | € 255 | € 200 | \$120 |
| Associate Director, Submissions               | \$355 | € 335 | € 260 | \$130 |
| Director, Submissions                         | \$380 | € 345 | € 270 | \$145 |
| Sr. Director, Submissions                     | \$425 | € 385 | € 305 | \$155 |
| Program Coordinators                          |       |       |       |       |
| Program Coordinator I                         | N/A   | € 125 | € 100 | N/A   |
| Program Coordinator II                        | \$200 | € 155 | € 120 | N/A   |
| Sr. Program Coordinator                       | \$235 | € 190 | € 150 | N/A   |
| VP, Reg Affairs, Head of Program Management   | \$520 | € 455 | € 405 | N/A   |
| Medical Writing                               |       |       |       |       |
| Medical Writer I                              | \$260 | € 210 | € 165 | \$105 |
| Medical Writer II                             | \$315 | € 255 | € 200 | \$115 |
| Sr. Medical Writer                            | \$355 | € 290 | € 225 | \$125 |
| Associate Director, Medical Writer            | \$400 | € 335 | € 300 | \$150 |
| Director, Medical Writing                     | \$435 | € 345 | € 310 | \$160 |
| Sr. Director, Medical Writing                 | \$475 | € 385 | € 350 | \$200 |
| GxP Strategy Consulting                       |       |       |       |       |
| GxP Associate I                               | \$260 | € 210 | € 165 | N/A   |
| GxP Associate II                              | \$315 | € 255 | € 200 | N/A   |
| GxP Strategy Manager                          | \$355 | € 290 | € 225 | N/A   |
| Associate Director, GxP Strategy              | \$400 | € 335 | € 300 | N/A   |
| Director, GxP Strategy                        | \$435 | € 345 | € 310 | N/A   |
| Sr. Director, GxP Strategy                    | \$475 | € 385 | € 350 | N/A   |
| VP, GxP Strategy                              | \$520 | € 455 | € 405 | N/A   |
| Regulatory and Drug Development Scientists    |       |       |       |       |
| Scientist                                     | \$260 | € 210 | € 165 | N/A   |
| Scientist I                                   | \$315 | € 255 | € 200 | N/A   |
| Scientist II                                  | \$355 | € 290 | € 225 | N/A   |
| Senior Scientist                              | \$380 | € 310 | € 240 | N/A   |
| Associate Director, Scientist                 | \$400 | € 335 | € 300 | N/A   |
| Director, Scientist                           | \$435 | € 345 | € 310 | N/A   |
| Sr. Director, Scientist                       | \$475 | € 385 | € 350 | N/A   |
| VP. Scientist                                 | \$520 | € 455 | € 405 | N/A   |
| Sr. Strategist, Division Head and SVP         | \$575 | € 500 | € 445 | N/A   |
| Medical Affairs                               |       |       |       |       |
| Medical Monitor                               | \$425 | € 355 | N/A   | N/A   |
| Medical Director                              | \$475 | € 415 | N/A   | N/A   |
| Sr. Medical Director                          | \$495 | € 430 | N/A   | N/A   |
| Executive Medical Director                    | \$545 | € 470 | N/A   | N/A   |
| Chief Medical Officer                         | \$585 | € 505 | N/A   | N/A   |
| Biostatistics                                 |       |       |       |       |
| Statistical Programmer (below Assoc Director) | \$285 | € 235 | N/A   | N/A   |

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|   | NA*   | WEU   | EEU  | IND* |
|---|-------|-------|------|------|
| Statistical Programmer (Assoc Director & Above) | \$390 | € 255 | N/A  | N/A  |
| Biostatistician (below Director)                | \$400 | € 330 | N/A  | N/A  |
| Biostatistician (Director & Above)              | \$440 | € 350 | N/A  | N/A  |
| Biometrics Project Coordination                 | \$180 | N/A   | € 50 | N/A  |
| <b>Pharmacometrist</b>                          |       |       |      |      |
| Pharmacometrist I                               | \$415 | N/A   | N/A  | N/A  |
| Pharmacometrist II                              | \$445 | N/A   | N/A  | N/A  |
| Sr. Pharmacometrist                             | \$460 | N/A   | N/A  | N/A  |
| Associate Director, Pharmacometrics             | \$485 | N/A   | N/A  | N/A  |
| Director, Pharmacometrics                       | \$505 | N/A   | N/A  | N/A  |
| Sr. Director, Pharmacometrics                   | \$555 | N/A   | N/A  | N/A  |
| VP, Pharmacometrics                             | \$595 | N/A   | N/A  | N/A  |
| <b>Pharmacokineticist</b>                       |       |       |      |      |
| Pharmacokineticist I                            | \$415 | N/A   | N/A  | N/A  |
| Pharmacokineticist II                           | \$445 | N/A   | N/A  | N/A  |
| Sr. Pharmacokineticist                          | \$460 | N/A   | N/A  | N/A  |
| Associate Director, Pharmacokinetics            | \$485 | N/A   | N/A  | N/A  |
| Director, Pharmacokinetics                      | \$505 | N/A   | N/A  | N/A  |
| <b>CPMS Programming</b>                         |       |       |      |      |
| Programmer I                                    | \$315 | N/A   | N/A  | N/A  |
| Programmer II                                   | \$340 | N/A   | N/A  | N/A  |
| Sr. Programmer                                  | \$370 | N/A   | N/A  | N/A  |
| Associate Director, Programming                 | \$410 | N/A   | N/A  | N/A  |
| Director, Programming                           | \$430 | N/A   | N/A  | N/A  |
| <b>CPMS Program Management</b>                  |       |       |      |      |
| Program Manager I                               | \$255 | N/A   | N/A  | N/A  |
| Program Manager II                              | \$305 | N/A   | N/A  | N/A  |
| Sr. Program Manager                             | \$320 | N/A   | N/A  | N/A  |
| Associate Director, Program Management          | \$335 | N/A   | N/A  | N/A  |
| Director, Program Management                    | \$405 | N/A   | N/A  | N/A  |
| <b>Clinical Pharmacology</b>                    |       |       |      |      |
| Fellow, Clinical Pharmacology                   | \$235 | N/A   | N/A  | N/A  |
| Technical Writer I                              | \$260 | N/A   | N/A  | N/A  |
| Technical Writer II                             | \$310 | N/A   | N/A  | N/A  |
| Clinical Pharmacologist I                       | \$415 | N/A   | N/A  | N/A  |
| Clinical Pharmacologist II                      | \$445 | N/A   | N/A  | N/A  |
| Sr. Clinical Pharmacologist                     | \$460 | N/A   | N/A  | N/A  |
| Associate Director, Clinical Pharmacology       | \$485 | N/A   | N/A  | N/A  |
| Director, Clinical Pharmacology                 | \$505 | N/A   | N/A  | N/A  |
| Sr. Director, Clinical Pharmacology             | \$555 | N/A   | N/A  | N/A  |
| VP, Clinical Pharmacology                       | \$595 | N/A   | N/A  | N/A  |

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### Certificate Of Completion

Envelope Id: 0F4B401CA2534E2B8B94EE606503BD4D Status: Completed  
 Subject: Complete with Docusign: Amalgent 17133 ACA 26Jun2024 - for signature.docx  
 Source Envelope:  
 Document Pages: 17 Signatures: 2 Envelope Originator:  
 Certificate Pages: 5 Initials: 0 Katherine Klusek  
 AutoNav: Enabled 450 N. Sam Houston Parkway E.,  
 EnvelopeD Stamping: Disabled Suite 250  
 Time Zone: (UTC-08:00) Pacific Time (US & Canada) Houston, TX 77060  
 Katherine.Klusek@allucent.com  
 IP Address: 162.201.20.241

### Record Tracking

Status: Original Holder: Katherine Klusek Location: DocuSign  
 6/26/2024 5:50:49 AM Katherine.Klusek@allucent.com

| Signer Events  | Signature   | Timestamp  |
|--|---|--|
| Malcolm A. Meyn<br>malcolm@amalgent.com<br>Security Level: Email, Account Authentication (Required), Logged in | <p>DocuSigned by:<br/> <br/> <b>Malcolm A. Meyn</b><br/>  Signer Name: Malcolm A. Meyn<br/>   Signing Reason: I approve this document<br/>   Signing Time: 26-Jun-2024   14:37 EDT<br/>   4EC522914E46464880F7DFF3C4FE4CE0</p> <p>Signature Adoption: Pre-selected Style<br/>   Signature ID: 4EC52291-4E46-4648-80F7-DFF3C4FE4CE0<br/>   Using IP Address: 136.54.35.19</p> <p>With Signing Authentication via DocuSign password<br/>   With Signing Reasons (on each tab):<br/>   I approve this document</p> | <p>Sent: 6/26/2024 5:52:16 AM<br/>   Viewed: 6/26/2024 11:36:42 AM<br/>   Signed: 6/27/2024 1:53:48 PM</p> |

#### Electronic Record and Signature Disclosure:

Accepted: 6/26/2024 11:36:42 AM  
 ID: d9608fa9-1278-4051-bcdd-5bb6ad70c651

|   |   |   |
|---|---|---|
| Howard Brand<br>howard.brand@allucent.com<br>VP Finance<br>Security Level: Email, Account Authentication (Required) | <br><p>Signature Adoption: Pre-selected Style<br/>   Signature ID: 87F9996B-564A-4D08-A25A-EA0996CC32F6<br/>   Using IP Address: 107.15.146.138</p> <p>With Signing Authentication via DocuSign password<br/>   With Signing Reasons (on each tab):<br/>   I approve this document</p> | <p>Sent: 6/27/2024 1:53:51 PM<br/>   Viewed: 6/27/2024 2:24:18 PM<br/>   Signed: 6/27/2024 2:24:33 PM</p> |
|---|---|---|

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|-------------------------|-----------|-----------|
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|--|------------------|----------------------|
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| Envelope Summary Events                    | Status           | Timestamps           |
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| Certified Delivered                        | Security Checked | 6/27/2024 2:24:18 PM |
| Signing Complete                           | Security Checked | 6/27/2024 2:24:33 PM |
| Completed                                  | Security Checked | 6/27/2024 2:24:33 PM |
| Payment Events                             | Status           | Timestamps           |
| Electronic Record and Signature Disclosure |                  |                      |

Electronic Record and Signature Disclosure created on: 8/21/2023 4:03:09 AM

Parties agreed to: Malcolm A. Meyn

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At any time, you may request from us a paper copy of any record provided or made available electronically to you by us. You will have the ability to download and print documents we send to you through the DocuSign system during and immediately after the signing session and, if you elect to create a DocuSign account, you may access the documents for a limited period of time (usually 30 days) after such documents are first sent to you. After such time, if you wish for us to send you paper copies of any such documents from our office to you, you will be charged a \$0.00 per-page fee. You may request delivery of such paper copies from us by following the procedure described below.

### **Withdrawing your consent**

If you decide to receive notices and disclosures from us electronically, you may at any time change your mind and tell us that thereafter you want to receive required notices and disclosures only in paper format. How you must inform us of your decision to receive future notices and disclosure in paper format and withdraw your consent to receive notices and disclosures electronically is described below.

### **Consequences of changing your mind**

If you elect to receive required notices and disclosures only in paper format, it will slow the speed at which we can complete certain steps in transactions with you and delivering services to you because we will need first to send the required notices or disclosures to you in paper format, and then wait until we receive back from you your acknowledgment of your receipt of such paper notices or disclosures. Further, you will no longer be able to use the DocuSign system to receive required notices and consents electronically from us or to sign electronically documents from us.

### **All notices and disclosures will be sent to you electronically**

Unless you tell us otherwise in accordance with the procedures described herein, we will provide electronically to you through the DocuSign system all required notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you during the course of our relationship with you. To reduce the chance of you inadvertently not receiving any notice or disclosure, we prefer to provide all of the required notices and disclosures to you by the same method and to the same address that you have given us. Thus, you can receive all the disclosures and notices electronically or in paper format through the paper mail delivery system. If you do not agree with this process, please let us know as described below. Please also see the paragraph immediately above that describes the consequences of your electing not to receive delivery of the notices and disclosures electronically from us.

**How to contact Allucent - Regulated Account:**

You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows:

To contact us by email send messages to: [Liaty.Port@allucent.com](mailto:Liaty.Port@allucent.com)

**To advise Allucent - Regulated Account of your new email address**

To let us know of a change in your email address where we should send notices and disclosures electronically to you, you must send an email message to us at [Liaty.Port@allucent.com](mailto:Liaty.Port@allucent.com) and in the body of such request you must state: your previous email address, your new email address. We do not require any other information from you to change your email address.

If you created a DocuSign account, you may update it with your new email address through your account preferences.

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- i. decline to sign a document from within your signing session, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;
- ii. send us an email to Liaty.Port@allucent.com and in the body of such request you must state your email, full name, mailing address, and telephone number. We do not need any other information from you to withdraw consent.. The consequences of your withdrawing consent for online documents will be that transactions may take a longer time to process..

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To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please confirm that you have read this ERSD, and (i) that you are able to print on paper or electronically save this ERSD for your future reference and access; or (ii) that you are able to email this ERSD to an email address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format as described herein, then select the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

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- You can access and read this Electronic Record and Signature Disclosure; and
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- Until or unless you notify Allucent - Regulated Account as described above, you consent to receive exclusively through electronic means all notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you by Allucent - Regulated Account during the course of your relationship with Allucent - Regulated Account.



## BIOANALYTICAL PROPOSAL NO. 136077-02

### Development, Validation, Stability and Analysis of Pramipexole in Human Plasma

**DATE:** 23 August 2024

This is an estimated Ballpark. PPD will conduct this study in our Middleton, Wisconsin laboratory.

| Task                       | Study Description  | Price       |
|----------------------------|--|-------------|
|                            | <b>R&amp;D</b>   |             |
| Development                | Development of a LC/MS/MS assay for the determination of Pramipexole in human plasma containing K2EDTA estimated to take up to 12 days at \$2,903 per day (will only be billed for time used).<br>Target Sample aliquot: =100µL<br>Target range: TBD   | \$34,836.00 |
| Validation                 | Validation of a LC/MS/MS assay for the determination of Pramipexole in human plasma containing K2EDTA.   | \$35,078.00 |
| Stability                  | Evaluation of long-term stability for Pramipexole in human plasma. One (1) long-term stability evaluation will be conducted during the validation experiments (less than or equal to one month) and is included in the validation fee. Additional stability will be charged at \$5,761 per time point. Three additional time points, at approximately 3, 6, and 12 months, at both -25 °C and -80 °C have been budgeted. | \$17,283.00 |
| Interference Check         | Interference check in the presence of Morphine and metabolites: (morphine-3-glucuronide and morphine-6-glucuronide) estimated to take up to two (2) days at \$2,903 per day.   | \$5,806.00  |
| Column Fee                 | Estimated \$2,000 for UPLC analytical columns. Will invoice only what is used.   | \$2,000.00  |
|                            | <b>Sample Analysis</b>   |             |
| Analytical (Pramipexole)   | LC/MS/MS analysis of 768 human plasma samples for pramipexole estimated at \$74.88 per sample.   | \$61,939.20 |
| Incurred Sample Reanalysis | Approximately 10% (77 samples) will be repeated to assess incurred sample reanalysis at \$80.65 per sample.  | \$6,210.05  |
| Reassays                   | An additional 10% (77 samples at \$80.65 per sample) has been included in the budget for potential bioanalytical reassays.   | \$6,210.05  |
| Column Fee                 | Estimated \$2,000 for UPLC analytical columns. Will invoice only what is used.   | \$2,000.00  |
| Analytical (Morphine)      | LC/MS/MS analysis of 768 human plasma samples for morphine and metabolites morphine-3-glucuronide and morphine-6-glucuronide, estimated at \$86.42 per sample.   | \$66,370.56 |
| Incurred Sample Reanalysis | Approximately 10% (77 samples) will be repeated to assess incurred sample reanalysis at \$86.42 per sample.  | \$6,654.34  |
| Interference Check         | Interference check in the presence of pramipexole estimated to take one (1) day at \$2,903 per day.  | \$2,903.00  |
| Reassays                   | An additional 10% (77 samples at \$86.42 per sample) has been included in the budget for potential bioanalytical reassays.   | \$6,654.34  |

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**Page 2**  
**Jason McPherson**  
**PPD Development, Inc.**  
**Proposal No. 136077-02**  
**23 August 2024**

|            |  |                     |
|------------|--|---------------------|
| Column Fee | Estimated \$2,000 for UPLC analytical columns. Will invoice only what is used. | \$2,000.00          |
|            | <b>Total</b>   | <b>\$255,944.54</b> |

\*These costs may vary depending on the actual amount of R&D time required and may exceed the estimated number of days at the quoted per day rate. Work beyond the estimated days will not be conducted without written permission of PPD Development, Inc.

CONFIDENTIAL AND PROPRIETARY INFORMATION

**Ballpark Estimate Details**

|                  |                       |
|------------------|-----------------------|
| Client           | Amalgent Therapeutics |
| BC#              | 136077-01             |
| Protocol         | AMGT-0220             |
| Therapeutic Area | Pain                  |

**Key Specifications**

|                |      |
|----------------|------|
| # Countries    | 1    |
| # Sites        | 1    |
| # Patients     | 12   |
| Study Duration | 10.3 |

| Service Area                             | Costs (USD)         |
|--|---------------------|
| Project Management                       | \$ 125,000          |
| Clinical Management                      | \$ 125,000          |
| Biostatistics                            | \$ 100,000          |
| Data Management                          | \$ 150,000          |
| Information Technology                   | \$ 10,000           |
| Medical Writing                          | \$ 75,000           |
| Pharmacokinetics                         | \$ 150,000          |
| Pharmacovigilance                        | \$ 75,000           |
| <b>GRAND TOTAL DIRECT COSTS</b>          | <b>\$ 810,000</b>   |
| <b>GRAND TOTAL PASS THROUGH EXPENSES</b> | <b>\$ 50,000</b>    |
| <b>INVESTIGATOR GRANTS</b>               | <b>\$ 1,500,000</b> |
| <b>BIOANALYTICAL LAB COSTS</b>           | <b>\$ 255,945</b>   |
| <b>BALLPARK ESTIMATE TOTAL</b>           | <b>\$ 2,615,945</b> |

\* Estimated costs are NON-BINDING

\* Estimated costs do not account for highly customized projects

\* The ballpark estimate maintains a deviation of +/- 15%. All costs are provided in USD. This ballpark estimate does NOT take into consideration inflation related adjustments; inflationary will be calculated and presented at time of formal proposal request.

Assumptions:

1 CRU

N=12 NHVs

Plan for an equal gender split

Aim to enroll in one group; however will plan for a second group given the requirement of the equal gender split

Subjects will be in-house (IH) Day -1 to Day 11, with a phone call (PC) on Day 15

PPD Proprietary &amp; Confidential

BC# 136077-01

22-Aug-24



August 30<sup>th</sup>, 2024

Dr. Malcolm A. Meyn  
Amalgent Therapeutics, Inc.  
300 E First St.  
Greenville, NC 27858.

Dear Dr. Meyn,

Foresight Science & Technology, Inc. (Foresight) will be delighted to serve as the Technical and Business Assistance (TABA) vendor for Amalgent Therapeutics, Inc. in support of your NIDA SBIR Fast-Track project proposal entitled "Clinical Development of the First Fixed Dose Combination Pain Therapeutic with Decreased Potential for Abuse and Tolerance."

Founded in 1980, Foresight is a world leading full-service provider of commercialization, technology transfer, due diligence, open innovation, and IP Management services. Our clients include universities, companies, government agencies, laboratories, foundations, and investors. Foresight supports or evaluates the commercial potential of more than 600 technologies per year in many different sectors, many of which are SBIR/STTR- funded technologies. Foresight has deep background and experience as a SBIR commercialization support contractor and is currently under contract to provide services for the EPA SBIR Phase I TABA program, the USDOT SBIR Phase I and II TABA Program, and is the Commercialization Plan reviewer for DOE SBIR/STTR Phase II proposals. Foresight's staff of over 70 Senior Consultants has domain expertise across all industries and are veterans of commercialization and product development with experience in research, technology transfer, new venture creation, and business development. Our experience gives us unique capabilities to look across many sectors and business models to accurately and creatively evaluate commercial potential, formulate strategies for market success, and guide innovations to market.

If awarded, Foresight will provide a combination of the following TABA services:

Phase I:

- Market Analysis reviewing competitive technologies, market size and dynamics
- Expert/End-User Interviews for market validation
- Identification of Potential Commercialization Partner Contacts (i.e. development partner, integrator, distributor, funding source, licensee)

Phase II:

- IP Landscape Review (legal services not provided)
- Market Entry Launch Strategy
- Preparation of Technology Marketing Material (i.e. pitch deck, technology flyer)
- Outreach to Potential Commercialization Partners
- Deal Terms and Licensing Advisory
- Fundraising Strategy Development

Foresight Science & Technology, Inc.  
34 Hayden Rowe Street Suite 156, Hopkinton, MA 01748-1889 USA  
Voice: 401-273-4844; Fax: 401-354-1301

These services will benefit you in validating your market, establishing contact with potential partners, and preparing for commercialization of the product resulting from this project. Foresight will complete the tasks listed above utilizing resources at a minimum qualification level of Senior Professional.\*

\*Senior Professional (description per GSA Contract 47QRAA19D0033)

*A Senior Professional serves as an expert consultant in strategic commercialization, negotiating, marketing and market introduction of new and emerging innovations and technologies. May perform this role as a team leader, trainer or individual. Capable of leading and/or reviewing work by others including that which is provided by the client. Responsible for schedules and deliverables as defined by the client contract. Experience includes all the following at a minimum:*

*Five years of experience in technology transfer or a related field, including three years of management or supervisory experience or similar military experience. Master's Degree. The individual has been certified as a market research or technology analyst through Foresight's formal certification process.*

The selected tasks will be performed during the NIDA SBIR Fast-Track Phase I and Phase II performance periods.

|                 |                              |                    |
|-----------------|------------------------------|--------------------|
| Phase I Budget: | 40 hours @ \$175.00 per hour | \$ 7,000.00        |
|                 | <i>Courtesy Discount</i>     | <i>(\$ 500.00)</i> |
|                 | <b>TOTAL</b>                 | <b>\$ 6,500.00</b> |

|                  |                               |                      |
|------------------|-------------------------------|----------------------|
| Phase II Budget: | 292 hours @ \$175.00 per hour | \$ 51,100.00         |
|                  | <i>Courtesy Discount</i>      | <i>(\$ 1,100.00)</i> |
|                  | <b>TOTAL</b>                  | <b>\$ 50,000.00</b>  |

Foresight attests that this rate is consistent with recent billings for similar work.

We wish you the best of success with your funding application and project.

Sincerely yours,



Alyssa Belleville, Director of Sales & Marketing  
 Foresight Science & Technology, Inc.  
 DUNS: 10-393-2240. UEI: GHG2Z3MBLGL6  
 alyssa.belleville@foresightst.com  
 1-401-273-4844 ext. 4004

Foresight Science & Technology, Inc.  
 34 Hayden Rowe Street Suite 156, Hopkinton, MA 01748-1889 USA  
 Voice: 401-273-4844; Fax: 401-354-1301

**RESEARCH & RELATED BUDGET - Cumulative Budget**

|  | Totals (\$)  |
|--|--------------|
| Section A, Senior/Key Person                     | 246,240.00   |
| Section B, Other Personnel                       | 0.00         |
| Total Number Other Personnel                     | 0            |
| Total Salary, Wages and Fringe Benefits<br>(A+B) | 246,240.00   |
| Section C, Equipment                             | 0.00         |
| Section D, Travel                                | 16,000.00    |
| 1. Domestic                                      | 16,000.00    |
| 2. Foreign                                       | 0.00         |
| Section E, Participant/Trainee Support Costs     | 0.00         |
| 1. Tuition/Fees/Health Insurance                 | 0.00         |
| 2. Stipends                                      | 0.00         |
| 3. Travel  | 0.00         |
| 4. Subsistence                                   | 0.00         |
| 5. Other   | 0.00         |
| 6. Number of Participants/Trainees               | 0            |
| Section F, Other Direct Costs                    | 2,722,900.00 |
| 1. Materials and Supplies                        | 10,000.00    |
| 2. Publication Costs                             | 0.00         |
| 3. Consultant Services                           | 229,500.00   |
| 4. ADP/Computer Services                         | 0.00         |
| 5. Subawards/Consortium/Contractual Costs        | 2,426,900.00 |
| 6. Equipment or Facility Rental/User Fees        | 0.00         |
| 7. Alterations and Renovations                   | 0.00         |
| 8. Other 1                                       | 0.00         |
| 9. Other 2                                       | 56,500.00    |
| 10. Other 3                                      | 0.00         |
| 11. Other 4                                      | 0.00         |
| 12. Other 5                                      | 0.00         |
| 13. Other 6                                      | 0.00         |
| 14. Other 7                                      | 0.00         |
| 15. Other 8                                      | 0.00         |
| 16. Other 9                                      | 0.00         |
| 17. Other 10                                     | 0.00         |
| Section G, Direct Costs<br>(A thru F)            | 2,985,140.00 |
| Section H, Indirect Costs                        | 137,935.00   |

|   |              |
|---|--------------|
| Section I, Total Direct and Indirect Costs<br>(G + H) | 3,123,075.00 |
| Section J, Fee  | 214,661.00   |
| Section K, Total Costs and Fee (I + J)                | 3,337,736.00 |

**SBIR/STTR Information**

Agency to which you are applying (select only one)\*

 DOE       HHS       USDA       Other:

SBC Control ID:\*

001689375

Program Type (select only one)\*

 SBIR       STTR Both (See agency-specific instructions to determine whether a particular agency allows a single submission for both SBIR and STTR)

Application Type (select only one)\*

 Phase I       Phase II       Fast-Track       Direct Phase II       Phase IIA       Phase IIB       Phase IIC Commercialization Readiness Program (See agency-specific instructions to determine application type participation.)

Phase I Letter of Intent Number:

\* Agency Topic/Subtopic:

Questions 1-8 must be completed by all SBIR and STTR Applicants:

1a. Do you certify that at the time of award your organization will meet the eligibility criteria for a small business as defined in the funding opportunity announcement?\*       Yes       No

1b. Anticipated Number of personnel to be employed at your organization at the time of award.\*      2

1c. Is your small business majority owned by venture capital operating companies, hedge funds, or private equity firms?\*       Yes       No1d. Is your small business a Faculty or Student-Owned entity?\*       Yes       No2. Does this application include subcontracts with Federal laboratories or any other Federal Government agencies?\*       Yes       No

If yes, insert the names of the Federal laboratories/agencies:\*

3. Are you located in a HUBZone? To find out if your business is in a HUBZone, use the mapping utility provided by the Small Business Administration at its web site: <http://www.sba.gov> \*       Yes       No4. Will all research and development on the project be performed in its entirety in the United States?\*       Yes       No

If no, provide an explanation in an attached file.      Explanation:\*

5. Has the applicant and/or Program Director/Principal Investigator submitted proposals for essentially equivalent work under other Federal program solicitations or received other Federal awards for essentially equivalent work?\*       Yes       No

If yes, insert the names of the other Federal agencies:\*

6. Disclosure Permission Statement: If this application does not result in an award, is the Government permitted to disclose the title of your proposed project, and the name, address, telephone number and email address of the official signing for the applicant organization to state-level economic development organizations that may be interested in contacting you for further information (e.g., possible collaborations, investment)?\*       Yes       No7. Does the application include a request of SBIR or STTR funds for Technical and Business Assistance (TABA)? If yes, please follow the agency specific instructions to provide the budget request and justification. (Please answer no if you plan to use the agency TABA vendor, which does not require you to include a request for TABA funds in your application.)\*       Yes       No

8. Commercialization Plan: The following applications require a Commercialization Plan: Phase I (DOE only), Phase II (all agencies), Phase I/II Fast-Track (all agencies). Include a Commercialization Plan in accordance with the agency announcement and/or agency-specific instructions.\*

Attach File:\*

CP\_Amalgent\_Final\_2024.09.04.pdf

## SBIR/STTR Information

### SBIR-Specific Questions:

Questions 9 and 10 apply only to SBIR applications. If you are submitting ONLY an STTR application, leave questions 9 and 10 blank and proceed to question 11.

9. Have you received SBIR Phase II awards from the Federal Government? If yes, provide a company commercialization history in accordance with agency-specific instructions using this attachment.\*

Yes  No

Attach File: [Commercialization\\_History\\_AT\\_ET\\_2024.08\\_30.docx.pdf](Commercialization_History_AT_ET_2024.08_30.docx.pdf)

10. Will the Project Director/Principal Investigator have his/her primary employment with the small business at the time of award?\*

Yes  No

### STTR-Specific Questions:

Questions 11 - 13 apply only to STTR applications. If you are submitting ONLY an SBIR application, leave questions 11 - 13 blank.

11. Please indicate whether the answer to BOTH of the following questions is TRUE:\*

Yes  No

(1) Does the Project Director/Principal Investigator have a formal appointment or commitment either with the small business directly (as an employee or a contractor) OR as an employee of the Research Institution, which in turn has made a commitment to the small business through the STTR application process; AND

(2) Will the Project Director/Principal Investigator devote at least 10% effort to the proposed project?

12. In the joint research and development proposed in this project, does the small business perform at least 40% of the work and the research institution named in the application perform at least 30% of the work?\*

Yes  No

13. Provide UEI of non-profit research partner for STTR.\*

## COMMERCIALIZATION PLAN

**Amalent Therapeutics, Inc. is developing AMGT-0220 as a first-line therapy to treat moderate to severe pain with a safer and non-addictive therapeutic profile. This project will advance the development of our first product, a novel fixed-dose combination therapeutic that provides pain relief at a significantly lower morphine dose than would typically be required while simultaneously mitigating the abuse potential of morphine.**

The proposed therapeutic leverages our discovery that pramipexole, a dopamine agonist approved for treating Parkinson's Disease, can act as a highly effective opioid adjuvant. Published data indicates that pramipexole in combination with a subtherapeutic dose of opioid should have a lower abuse potential than opioids alone by a) preventing opioid tolerance b) reducing opioid withdrawal symptoms, and c) lowering the effective dose for acute pain <sup>1,2</sup>.

Amalent Therapeutics' primary commercialization goal is to seek an NDA for a fixed-dose combination of pramipexole and morphine. The doses of morphine in this combination will be lower than are currently available or considered therapeutic. As our product comprises two FDA-approved therapeutics, we will utilize the 505(b)2 regulatory pathway, substantially decreasing risk and accelerating the time to approval. This application will support this goal by supporting an IND filing and Phase 1 of AMGT-0220's clinical trials.

### Value of the SBIR/STTR Project, Expected Outcomes, and Impacts

Managing the risk-benefit profile of opioid therapeutics is a significant challenge for today's physicians. For patients that do not respond to other pain therapies, opioids remain the standard of care. Despite the excellent analgesic properties of this class of drugs, significant risks accompany opioid use. Most notably, opioid prescriptions present the risk of misuse, abuse, and addiction. Over 2.4 million Americans currently have an opioid use disorder, and approximately 80,000 of these patients die per year <sup>3-9</sup>. The yearly economic cost to America due to opioid use disorder and fatal overdoses on opioids was estimated at over \$1 trillion <sup>10,11</sup>. Current medical guidelines call for minimizing opioid doses in those cases where opioids are required <sup>12,13</sup>. Yet, this can leave the most severe patients with untreated pain, and these guidelines have resulted in only a minimal decrease in opioid doses.

Replacing opioids has proven to be a challenging objective to execute. High-dose combinations of non-opioid analgesics have reduced the need for opioids for some patients but are far from becoming an opioid replacement. Vertex held significant hopes for VX-548 as a potential non-opioid pain treatment, but the compound ultimately failed to meet the endpoints necessary to position it as a viable alternative to opioid medications. The clinical trials revealed that VX-548 did not demonstrate the expected efficacy in pain management, falling short in key measures of pain relief and patient outcomes <sup>14</sup>. Consequently, VX-548 could not fulfill the stringent criteria required to offer a safer, effective solution for pain relief, which remains a critical need in the ongoing efforts to address the opioid crisis. The development pipeline lacks potential replacements: aside from VX-548, there are currently no ongoing Phase 3 clinical trials for new molecules listed on clinicaltrials.gov (searched July 2024).

Other options are limited. Zynrelef, a single-use gel combination of the anesthetic bupivacaine and the NSAID meloxicam, was approved in 2021 to manage postoperative pain. Clinical studies of Zynrelef showed a total opioid decrease of 18% in the 72 hours immediately following surgery <sup>15</sup>. While significant, most patients still required an opioid immediately after and in the days following surgery. Non-pharmaceutical interventions may help decrease overall opioid use. These include acupuncture, psychological and physical therapy, and medical devices. These pain relief strategies are still in early development and generally are targeted at chronic pain, leaving few options for those suffering from acute pain.

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*"Minimizing the opioid doses needed for effective pain relief will have a direct and immediate impact on my patients, allowing many of them to enjoy better pain relief and quality of life. In my experience, even a 10% decrease in opioid dose would be meaningful."*

*Paola A. Gehrig, MD  
Division Director, Gynecologic Oncology  
UNC Health*

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Short of identifying a total replacement for opioids, combining opioids with effective adjuvants provides the most significant immediate opportunity for decreasing opioid use. A pre-formulated, FDA-approved opioid-adjuvant combination therapeutic will reduce physician concerns about drug interactions and provide convenience to patients. An approved combination will also shift the task of ensuring physician awareness of opioid-adjuvant therapeutics from Continuing Medical Education providers to manufacturers of combination dosage forms, many of whom excel in messaging effectiveness.

We believe that an FDA approved pramipexole:morphine fixed-dose combination therapeutic will be a direct replacement for existing opioid monotherapies. In turn, this product could have an immediate positive effect on the opioid epidemic by decreasing the number of patients getting addicted to prescription opioids. The following section outlines the commercial impact of the specific aims proposed in this Fast Track SBIR project. The goal and expected outcomes of this application are to submit an IND application and conduct first-in-human Phase 1 pharmacokinetic (PK) study in healthy volunteers.

**Phase I – Aim 1: Manufacture clinical batches of AMGT-0220 drug product.** The objective of this aim is to prepare clinical batches of low-dose and high-dose AMGT-0220 to provide sufficient doses of AMGT-0220 for clinical trials. *Milestones: Complete manufacturing of clinical batches; pass release criteria.*

**Aim 2: Submit an IND application for AMGT-0220.** The objective of this aim is to prepare the IND application needed to proceed with first-in-human studies. *Milestones: Complete preparation of IND package; submit IND application.*

**Go/No Go for Phase II:** FDA receives IND package.

**Phase II – Aim 1: Conduct a Phase 1 single-dose PK clinical trial in healthy volunteers.** In this aim, we will conduct a human study to determine safety, efficacy and optimal dosing for further clinical trials. *Milestones: Determine bioequivalence and safety of AMGT-0220 in healthy volunteers*



**Figure 1: SBIR position in path to commercialization**

**Commercial Impact:** This Fast-Track project will provide PK data for further clinical trials, critical for regulatory approval, leading to commercialization of AMGT-0220 (Figure 1).

## Company Overview

### Corporate Structure and Mission

Amalent Therapeutics, Inc. is a privately-owned pharmaceutical company located in Greenville, NC. The Company was founded in February 2020 by Mr. Sam Tetlow and Dr. Malcolm Meyn based on discoveries made at East Carolina University. A team of scientists there discovered a serendipitous synergistic effect of an adjuvant active ingredient when combined with an opioid drug. The combination of these two active ingredients yields similar analgesia as commonly prescribed opioids but at dramatically reduced doses <sup>1,2</sup>. The combination also mitigates morphine addiction risk, prevents opioid tolerance, treats neuropathic pain. By reducing the dose, side effects of the opioid active ingredient are also reduced resulting in a highly attractive product profile. East Carolina University filed U.S. and PCT applications with broad methods and composition claims surrounding this invention.

*"Development of this technology into an FDA-approved therapeutic will have a significant impact on patients by **providing effective pain relief while minimizing the potential for addiction and other side effects.**"*

*Robert W. Hurley, MD, PhD  
Pain Management, Spine  
Wake Forest University*

The founders recognized that there is a high unmet need in medicine caused by poorly performing medications for severe pain, and a large opportunity to address these performance issues with the inventions made at the University. Amalgent holds the worldwide exclusive license to those patent applications, to develop combination pain therapeutics with a superior product profile to the approved pain medications that are currently marketed. The Company intends to develop a portfolio of combination pain therapeutics based on generic active ingredients on the market today. Each of these combinations builds on FDA-approved generic drugs that enjoy multibillion-dollar market segments in the United States.

***Addiction effects are reduced by significantly lowering dose while maintaining a therapeutic window AND by mitigating opioid reward seeking behavior and preventing the development of opioid tolerance.***

Because the Company begins with novel claims on FDA-approved medications, the 505(b)2 regulatory pathway will be pursued. In 2029, the Company expects to achieve FDA approval of the first combination of oral doses of morphine and pramipexole.

#### Management Team

**Sam Tetlow, MBA** — As co-founder, President and Chair of Board of Amalgent, Sam Tetlow has more than 30 years of experience exemplified by first-rate accomplishments and excellent qualifications. He has successful experience as an entrepreneur and investor in life sciences companies such as EpiCypher (named best University Startup of 2016 by U.S. Congress), ILS Genomics, Immunologix, Gentris Corporation, and Tranzyme Pharma (IPO April, 2011) among others. As a leader within companies Sam has a functional focus on product development, sales, finance and corporate development. Sam continues to build on his venture capital experience by investing into compelling companies as an Angel. Sam seeks results and has a proven track record. Sam has generated a 5.8x return on invested capital, with 76% cash realization in his last 14 years of investing.

**Malcolm A. Meyn, PhD, MSHS** — As co-founder and Chief Scientific Officer, Malcolm Meyn oversees all research and development programs, supports business development, assists in strategic decision making, and sits on the Board of Directors. He began his career as an academic scientist researching the complex systems that regulate how cells and organisms respond to chemical signals. In 2011, he joined Stemnion Therapeutics (now Noveome) in Pittsburgh, PA as director of non-clinical research and development. In this position he oversaw all aspects of preclinical work including safety studies, manufacturing studies, quality control, and efficacy. He contributed to pre-IND and IND preparation and interacted with the FDA in multiple meetings. In 2015 he started a consulting company in Chapel Hill, NC where he works with early-stage companies on product development strategies.

**Gerald Klein, MD** — Serving at Amalgent's Chief Medical Officer, Gerald Klein, M.D. is an accomplished expert in pain therapeutic drug development, with roles as Chief Medical Officer at companies like Oxygen Biotherapeutics, Talecris/Grifols, and Entera Health. He specializes in developing therapeutics that focus on pain conditions, including dental pain, arthritic pain, headaches, migraines, and central pain syndrome. Dr. Klein's work extends to neurology and psychiatry, covering conditions like migraines, epilepsy, and stroke. His experience includes clinical research, medical monitoring, and pharmacovigilance, contributing to the development and commercialization of pain therapies. He has served as an adjunct professor and has been actively involved in numerous peer-reviewed publications and international conferences. Dr. Klein's leadership in clinical trials and medical affairs has been pivotal in advancing pain management therapies in the field and is well suited to advance AMGT-0220.

**Andrew Graham, CFO** — Andrew Graham is a deeply experienced financial executive with extensive experience raising equity in the biotechnology and therapeutics sectors. He provides CFO and strategic financial advice for Amalgent. His previous roles include CFO at GemPharmatech, AgBiome, Advanced Animal Diagnostics, Trimeris, and Chief Restructuring Officer at Sicel Technologies. Graham's expertise encompasses strategic financial planning, corporate accounting, investor relations, and fundraising. His career highlights include raising capital, managing SEC filings, and overseeing financial operations for multiple therapeutics companies.

#### Company Advisors and Legal Counsel

**Frank Porreca, Ph.D.** Dr. Porreca is Associate Department Head of Pharmacology at the University of Arizona. He also holds Professorships in Anesthesiology, Cancer Biology, and Neuroscience. Dr. Porreca is a world recognized expert in the physiology of pain and the pharmacology of pain therapeutics. He is on Amalgent's

scientific advisory board, and advises on the design and analysis of non-clinical efficacy and safety studies.

**Gillian Schmitz, MD.** Dr. Schmitz is a board-certified Emergency Physician and an Associate Professor of Military and Emergency Medicine Uniformed Services University of the Health Sciences as well as the Vice Chair of Education, Brooke Army Medical Center. She is on the scientific advisory board and advises on emergency medicine aspects of pain management.

**Charles Argoff, MD.** Dr. Argoff is a professor of Neurology and the director of the Comprehensive Pain Program at Albany Medical Center. As a luminary in the field of pain management, Dr. Argoff has consulted with the leading firms in the field and remains a key opinion leader in the domain of leading pain management. He is on the scientific advisory board and advises on clinical strategy and product label design.

**Peter Barton Hutt.** Mr. Hutt is the former chief counsel for the FDA and is currently a senior attorney at Covington & Burling LLP, specializing in Food and Drug Law. He has experience with the FDA and helped draft legislation to create the National Institute of Alcohol Abuse and Alcoholism and the National Institute of Drug Abuse. He is on the scientific advisory board for Amalgent.

**Tim Wright.** Mr. Wright has been president of Mallinkrodt Pharmaceuticals and EVP of Corporate Strategy for Teva Pharmaceuticals pain division. Wright is a proven executive and healthcare industry veteran with more than 30 years of experience in the pharmaceutical, biotech and medical devices industries. In 2020 he was named as one of PM360 Magazine's 100 Most Influential People in the Healthcare Industry as an ELITE Transformational Leader. He has served in executive leadership of numerous pharmaceutical companies. He is a strategic advisor for Amalgent.

**Robert Hurley, MD.** Dr. Hurley is Professor of Anesthesiology and Public Health, Wake Forest University, Winston-Salem, North Carolina. He also serves as Executive Director of the Pain Service Line at Wake Forest Baptist. He has extensive experience in the translation of new technologies to the clinic. He advises Amalgent on the clinical aspects of pain management and clinical trial design.

**Medical and Regulatory Consulting** is provided by Allucent, a specialty CRO that provides a variety of consulting services for drug development and was co-founded by a team of scientists and entrepreneurs. Premier was selected as they have deep experience in combination therapeutics and pain as an indication, as well as the 505(b)2 pathway.

**Legal Counsel**—Amalgent is represented on corporate legal matters and licensing by David Wilke, Partner, with Wyrick Robbins Yates & Ponton (Raleigh, NC). For intellectual property, Amalgent is represented by Stanek Lemon Crouse & Meeks (Raleigh, NC). Our patent attorneys at Stanek Lemon include Shawna Canon Lemon, Ph.D., co-managing shareholder. She is a trained scientist in addition to being legal expert and has extensive experience guiding I.P. protection for drug development and drug technology companies.

**CMC and Quality Consulting** is provided by SciLucent, a consulting firm with deep experience in regulatory approval.

### History of Funding

Amalgent has received investment from funds and individuals who are on the front line of opioid treatment including emergency room physicians and Angel funds who have followed the progression of the technology over its years of development. To date, Amalgent has raised \$0.9 million in a convertible note round of financing that will convert into the Series A round. Amalgent is currently raising a \$5 million financing that will fund the Company through to its first IND and Phase 1 trial. The company also received a \$10,000 award as a finalist in a regional North Carolina life sciences competition in 2022 and a competitive \$250,000 loan from the North Carolina Biotechnology Center.

Amalgent was awarded a \$2.5 million Phase II SBIR from the National Institute on Drug Abuse (1R44DA059302-01). This grant supports the CMC work that will be included in the proposed IND. Prior to incorporation, Amalgent's technology received over \$5 million in research funding through various mechanisms at Eastern

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*"Approval of an opioid-minimizing medication will have a significant impact on the adverse effects associated with this therapy, including respiratory depression and addiction."*

*Frank Porecca, PhD*

Carolina University. As a Company, Amalgent Therapeutics is a pre-revenue drug product development company.

### Plan to Develop from a Small Technology R&D Business to a Successful Commercial Entity

Amalgent is focused on pain indications and intends to build a specialty pharmaceutical company with a focused commercialization team to market to pain medication high prescribers. At the same time, Amalgent will also be a very attractive acquisition target for large pharmaceutical companies with existing, problematic opioid franchises. These companies include Allergan, Daiichi-Sankyo, Endo, Hikma, Kyowa Kirin, Viatris (Mylan), Pfizer, and Teva.

Amalgent is currently raising a \$40 million round of equity financing that will fund all activities through the completion of a Phase II efficacy study for AMGT-0220 and initial development of a second therapeutic indicated for the treatment of chronic pain. Later, product development will be fueled by revenues from product licensing deals with pharma partners for the patent-protected products that we develop. Approval of this SBIR would signal the research community's approval of the technology and would improve our regulatory path, which would complement the business community's involvement. After establishing a consistent revenue stream, we will likely seek to develop our own products and carry them through regulatory approval in a variety of markets and partner with other companies to market and/or sell the products. With several patent-protected products in hand, Amalgent will be an attractive candidate for acquisition by a larger pharma partner within 3 to 5 years.

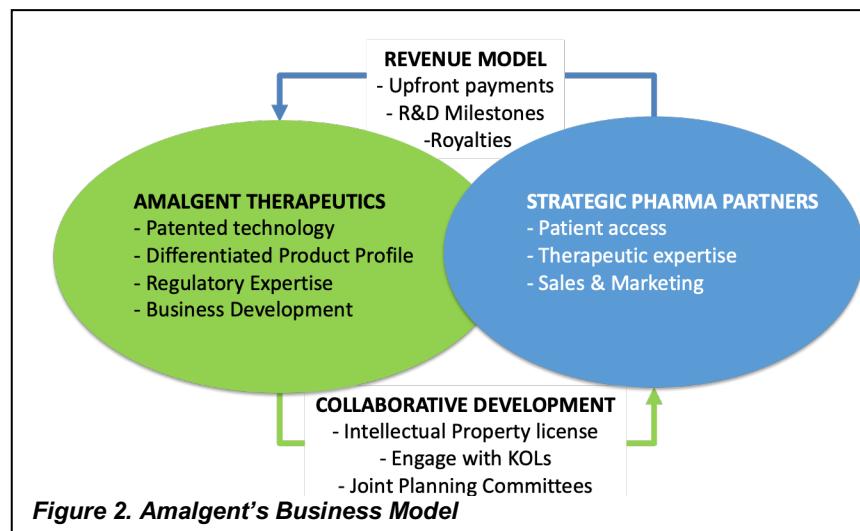
**The support provided by this SBIR will be instrumental in developing direct replacements for currently marketed opioid medications.**

### Strategic Decision to Target Oral Formulations of Combination Medications

Although our IP gives us exclusive rights to any therapeutic combination and formulation of opioids and D3 receptor agonists, we have focused our initial product development effort on an acute indication for a morphine/pramipexole combination for three reasons. First, morphine is the standard against which all other opioids are measured. Next, we have both animal and human data suggesting the efficacy of this combination. Third, starting in acute vs. chronic pain will hasten the product to market. We will develop the technology to treat chronic pain, additional methods of administration, and other active ingredient combinations. However, the road to approval for those products is much longer and holds more risk than this first combination.

**Figure 2** gives an overview of our business model. We will develop oral formulations of combination pain therapeutics for the US market and to maximize the market saturation of those medications here. At the same time, the Company will co-develop combinations for use in other geographies and other methods of administration such as intravenous and transdermal. We will generate revenue through strategic pharma partnerships in the form of upfront payments, milestone payments, and royalties on sales. We have developed and licensed intellectual property protecting our combination therapy and will continue to do so. Either independently or in consultation with partnering companies, we will continue to develop combination therapeutics that can provide meaningful clinical benefits (i.e., minimizing the dose necessary for pain relief, to minimize side effects including addiction.)

Although the total cost to develop each combination product may vary, the total cost from formulation to marketing can be estimated at over \$60M. We expect to develop products through the IND stage and early clinical stages (e.g., perhaps through Phase 2b trials). For each combination and geographic market, we intend to out-license our assets to pharmaceutical company partners. Our partners will provide the capital for product development, clinical testing, regulatory filing, and sales and marketing. We expect pre-deal development will cost Amalgent approximately \$10,000,000 per product through completion of Phase 2 clinical studies. Co-development deals

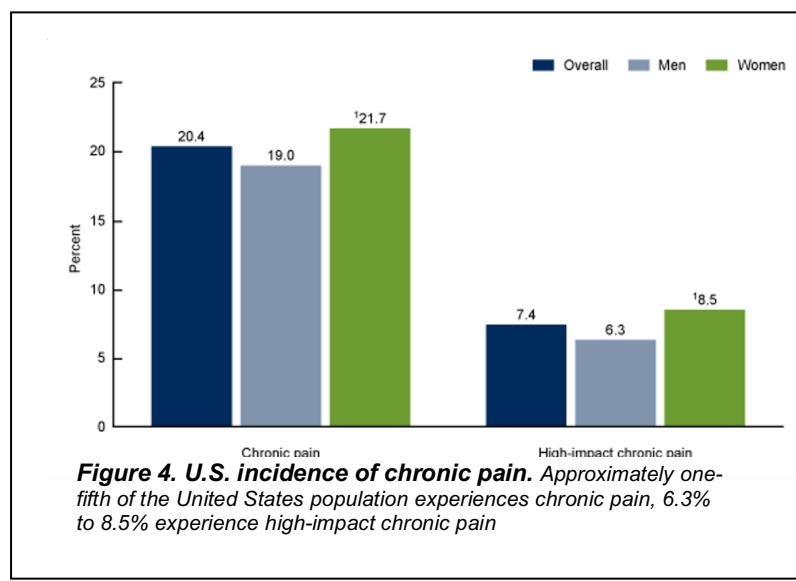
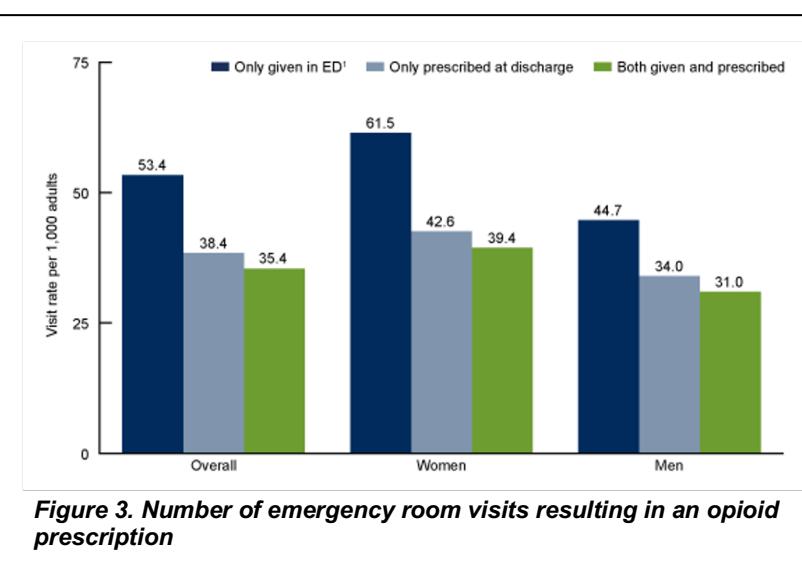


will likely include milestone and royalty payments, which will be determined by the clinical benefits and market size. Such payments will vary between different agreements, but the lower costs of development with the 505(b)2 pathway, coupled with fewer risks and technical hurdles, is expected to justify the use of Amalgent products vs. competing products (morphine or oxycodone monotherapy).

## Market, Customer, and Competition Analysis

### Scope of the problem

The pain market can be divided into acute and chronic. Acute pain occurs suddenly, lasts less than three months, and is usually a result of events such as trauma or surgery. Post-surgical pain alone is a significant challenge. Approximately 48.3 million surgical procedures are performed per year in the United States<sup>16</sup>. Of these patients, about 56% will receive postoperative opioids<sup>17</sup>. Each year, nearly 150 million people visit an emergency room in the United States. Of these, an average of 8.1% of patients are given an opioid prescription at discharge (Figure 3.)<sup>18,19</sup>.



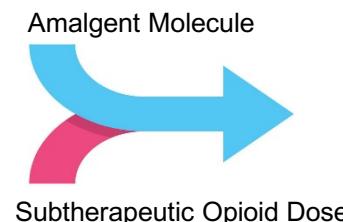
Chronic pain is pain lasting longer than three months and is one of the most common reasons adults seek medical care (Figure 4). An estimated 20.9% (or 51.6 million) of U.S. adults suffer from chronic pain with 6.9% (or 17.1 million) diagnosed with high impact chronic pain that has a significant impact on patient lifestyle<sup>20,21</sup>.

The implications of the large number of opioids prescribed each year are significant. The most notable complication of opioid use is addiction. A recent meta-analysis suggested that the pooled risk of prolonged opioid use after surgery was 6.7%<sup>22</sup>. Approximately 0.6% of patients developing a dependence after being prescribed an opioid for acute pain<sup>17</sup>. For surgical patients alone, this translates to over

150,000 new addictions per year. The statistics for chronic pain are significantly worse with between 8 and 12 percent of people using opioids for chronic pain developing an opioid use disorder<sup>23,24</sup>.

The costs of opioid addiction are significant. Many patients that develop an opioid use disorder following prescription drug use resort to off label use and street opioids such as fentanyl and heroin. Over 100,000 overdose deaths occurred in 2023, a significant increase from 70,000 in 2019<sup>25</sup>. This human cost also comes with an extensive financial cost of over \$504 billion per year in lost productivity and medical care. Current medical guidelines call for minimizing opioid doses in those cases where opioids are required<sup>12,13</sup>.

Beyond addiction, opioid use is associated with other significant side effects. So called "quality of life" side effects can significantly hinder the ability of patients to carry out daily activities. In a recent clinical study, 79% of patients prescribed an opioid for post-surgical pain reported a side effect<sup>26</sup>. The most common reported side effects included constipation, nausea/vomiting, dizziness,



### Competitive Advantages

1. *Addresses Addiction:* Reduces abuse potential
2. *Prevents opioid tolerance*
3. *Effective Pain Treatment with Fewer side effects*

**Figure 5: Competitive advantages of AMGT-0220**

drowsiness, sweating, and weakness. The reported incidence of most of these symptoms increased with higher dose levels.

### Target market size

The U.S. and global market for opioid drugs is large and continues to grow. The global market is valued at \$22.8 billion as of 2022 and is projected to grow to \$25 billion by 2030<sup>27</sup>. A rise in emergency rooms due to trauma and the continued growth in annual surgical procedures is driving acute pain market. Increases in the prevalence of cancer pain, lower back pain, and arthritis are driving the chronic pain market. Market limiters are decreasing prescriptions and a shift towards non-opioid pain therapy in the treatment of chronic pain.

| Company                            | Symbol | Sales (m\$) | Market Cap (m\$) | P/E  | P/S  | Pain products             |
|------------------------------------|--------|-------------|------------------|------|------|---------------------------|
| Johnson & Johnson                  | JNJ    | \$ 82,059   | \$ 365,515       | 21.8 | 4.5  | Actiq, Duragesic, Nucynta |
| Pfizer                             | PFE    | \$ 51,750   | \$ 197,992       | 23.2 | 3.8  | Demerol                   |
| Kyowa Kirin (ProStrakan)           | 4151.T | \$ 29,207   | \$ 168,807       | 41.5 | 5.8  | Abstral                   |
| AbbVie (Allergan)                  | ABBV   | \$ 32,226   | \$ 141,928       | 17.8 | 4.4  | Kadian                    |
| Teva Pharmaceuticals               | TEVA   | \$ 16,887   | \$ 9,840         | -    | 0.6  | Fentora                   |
| Hikma Pharmaceuticals              | HKMPY  | \$ 2,207    | \$ 7,668         | 16.5 | 3.5  | Roxanol-T                 |
| Mylan NV                           | MYL    | \$ 11,500   | \$ 7,333         | 27.1 | 0.6  | Ultram                    |
| Endo Pharmaceuticals               | ENDP   | \$ 2,914    | \$ 1,179         | -    | 0.4  | Opana, Percocet           |
| Indivior plc                       | INVVY  | \$ 785      | \$ 1,053         | -    | 1.3  | Suboxone, Sublocade       |
| Amneal Pharmaceuticals (Impax)     | AMRX   | \$ 1,626    | \$ 659           | -    | 0.4  | generics                  |
| Collegium Pharmaceuticals          | COLL   | \$ 297      | \$ 624           | -    | 2.1  | Xtampza ER                |
| Osmotica Pharma (Vertical)         | OSMT   | \$ 240      | \$ 340           | -    | 1.4  | Conzip, Lorzone           |
| BioDelivery Sciences International | BDSI   | \$ 111      | \$ 314           | 50.2 | 2.8  | Belbuca                   |
| Assertio Therapeutics (Egalet)     | ASRT   | \$ 229      | \$ 71            | -    | 0.3  | Oxyado                    |
| Mallinckrodt                       | MNK    | \$ 3,163    | \$ 63            | -    | 0.0  | Methadose                 |
| Daiichi Sankyo                     | DSNKY  | \$ 970      | \$ 49            | 26.0 | 0.1  | Morphabond                |
| Kempharm                           | KMPH   | \$ 13       | \$ 44            | -    | 3.4  | Apadaz                    |
| Acura Pharmaceuticals              | ACUR   | \$ 3        | \$ 39            | 13.0 | 13.0 |                           |
|                                    |        |             |                  | 15.8 | 2.7  |                           |

**Figure 6. Competitors and partners with significant pain franchises**

### The market is dominated by generics despite a widely recognized unmet need

This market is dominated by opioids. Five generic active ingredients account for almost 90% of the market. Almost all new approved pain therapeutics over the last 20 years have been for reformulations of existing opioid. In the past ten years, the only new molecule approved for the treatment of moderate to severe pain is the opioid Olynvik and there are few opioid replacements in the pipeline. The market is ready for disruption. Amalgent Therapeutics' solution offers a competitive advantage over opioid therapeutics dominating the market. AMGT-0220 combines a lower dose of opioids with a dopamine 3 receptor agonist. This solution has reduced abuse potential, prevents opioid tolerance, and has fewer side effects than the competition (**Figure 5**).

### Competitors/Partners/Acquirers

Amalgent Therapeutics is developing therapeutics against severe pain that are direct replacements for all opioids currently on the market. The current competitors are also natural partners. They can be broadly characterized in two classes: global integrated pharmaceutical companies and specialty pharmaceutical companies. See **Figure 6** for an analysis of current competitors/partners. Those shaded in blue are specialty pharma, and likely partners for some sublicensing only.

### Commercializing pain medications with a superior product profile

Improved medications for severe pain are an attractive opportunity for large global pharmaceutical companies, as well as a specialty company. While Amalgent will not pursue allocating the resources to commercialize improved medications to all physicians, most severe pain is addressed by specialists as shown in **Figure 7**.

The market for severe pain medications is concentrated with those physicians that prescribe these medications highly due to the nature of their practices. **Figure 7** demonstrates that these 170,000 US physicians will be the target commercialization market for Amalgent in the United States.

| Specialty                            | Amalgent docs |
|--------------------------------------|---------------|
| Sports Medicine (Orthopedic Surgery) | 2,457         |
| Vascular Surgery                     | 3,384         |
| Interventional Cardiology            | 3,475         |
| Thoracic Surgery                     | 4,052         |
| Pain Medicine and Pain Management    | 5,003         |
| Neurological Surgery                 | 5,053         |
| Plastic Surgery                      | 6,813         |
| Critical Care Medicine               | 9,932         |
| Hematology and Oncology              | 12,926        |
| Orthopedic Surgery                   | 18,069        |
| General Surgery                      | 21,644        |
| Anesthesiology                       | 38,960        |
| Emergency Medicine                   | 38,964        |
|                                      | 170,732       |

**Figure 7. Physicians in the United States, by specialty to be targeted by Amalgent**

## Formulation drives product differentiation and pricing

There is some differentiation between these drugs, driven by formulations and method of administration (**Figure 8**). Desperate for new ways to treat pain, the FDA continues to approve new opioid formulations. Examples include Dsuvia, a tablet formulation of sufentanil, and Xtampza, an abuse deterrent formulation of oxycodone. Amalgent is developing a patented fixed-dose combination drug that is differentiated from all of these other monotherapies by featuring an adjuvant as an active ingredient in addition to an opioid.

- |   |   |
|---|---|
| • Abstral (fentanyl) - ProStraken                           | • Olynvyk (oliceridine) – Trevena               |
| • Actiq (fentanyl) - J&J                                    | • Onsolis (fentanyl) - J&J                      |
| • Butrans ( <b>buprenorphine</b> transdermal system) - Teva | • Opana (oxymorphone) - Endo                    |
| • Conzip (tramadol) - Vertical                              | • Oramorph ( <b>morphine</b> ) - Xanodyne       |
| • Demerol (meperidine) - Pfizer                             | • Oxaydo ( <b>oxycodone</b> ) - Egalet          |
| • DSUVIA (Sufentanil) - AcelRx Pharmaceuticals              | • OxyContin ( <b>oxycodone</b> ) - Purdue       |
| • Dilaudid (hydromorphone) - Purdue                         | • Percocet ( <b>oxycodone</b> ) - Endo          |
| • Dolophine (methadone hydrochloride tablets) - Lilly       | • Roxanol-T ( <b>morphine</b> ) - Xanodyne      |
| • Duragesic (fentanyl transdermal system) - J&J             | • Sublimaze (fentanyl) - Akorn                  |
| • Fentora (fentanyl) - Teva                                 | • Ultram (tramadol) - Mylan                     |
| • Hysingla (hydrocodone) - Purdue                           | • Vicodin (hydrocodone) - Purdue                |
| • Kadian ( <b>morphine</b> ) - Allergan                     | • Xtampza ER ( <b>oxycodone</b> ) - Collegium   |
| • Methadose (methadone) - Mallinckrodt                      | • Zohydro ER (hydrocodone) – PersoN             |
| • Morphabond ( <b>morphine</b> ) - Daichi Sankyo            | • Zubsolv – ( <b>buprenorphine</b> ) – Orexo AB |
| • Nucynta ER (tapentadol) - J&J                             |   |

**Severe pain therapeutics are based on generic active ingredients.  
Amalgent provides alternatives to traditional opioids for physicians and patients.**

**Figure 8. Competition branded drugs with active ingredient**

## Market entry challenges

This SBIR project is designed to address the primary barrier to market entry: demonstrating safety and efficacy, completing clinical trials, and gaining regulatory approval. As both of the components of AMGT-0220 are already approved therapeutics separately, we will utilize the 505(b)2 regulatory pathway toward ultimate filing of an NDA. The specific aims of this SBIR will advance the program into clinical trials towards commercialization.

## **Intellectual Property (IP) Protection**

Amalgent has taken a worldwide exclusive license to inventions made by Kori Brewer, Ph.D. and Stefan Clemens, PhD. of East Carolina University. The University is pursuing patents with the United States, Canada, and Europe. We have two published US patents: #11,202,777 and #11,925,635. These are described in the RS. A third has been filed (**Figure 9**).

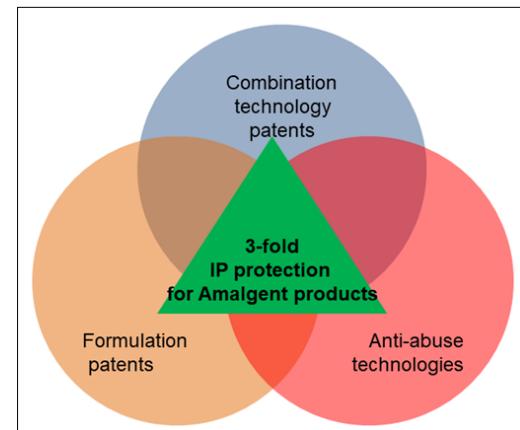
| Title   | Inventors                   | Filing Date | Serial Number |
|---|-----------------------------|-------------|---------------|
| Methods and compositions for maintaining opioid efficacy in the treatment of pain | Kori Brewer, Stefan Clemens | 10/25/2018  | 16/758,584    |
| Methods and compositions for maintaining opioid efficacy in the treatment of pain | Kori Brewer, Stefan Clemens | 12/20/2021  | 17/556,132    |
| Methods and compositions for maintaining opioid efficacy in the treatment of pain | Kori Brewer, Stefan Clemens | 2/16/2024   | 18/443,447    |

**Figure 9: Patents licensed by Amalgent**

Further, the Company expects two additional pieces of intellectual property to be incorporated into a final product for regulatory approval and commercialization. First, specific formulation work enables each combination and method of administration; formulation discoveries and/or licenses are critical to the completion of trials and commercialization. Second, it is expected that FDA will insist on some anti-abuse technology to be incorporated in the final product. Licenses to this kind of technology will be sought (**Figure 10**).

## Finance Plan

Amalgent is currently raising a financing round of up to \$40 million in a Series A financing that will fund operations through the Phase 2 studies for the first combination and beginning work on the next two combination pain medications. A total of \$40 million will be required to complete two pivotal Phase 3I trials on the first combination and advance two additional pramipexole: opioid combinations into the clinic. This amount will likely be generated through a combination of partnership payments and equity capital. Because the first approvals will be sought for acute indications, both phases for the first combination are expected to take four years in total.



**Figure 10. Multi-level IP protection for Amalgent products**

## Production, Regulatory, and Marketing Plan

### Production

Amalgent has engaged Catalent to formulate and manufacture clinical quantities of oral doses of the pramipexole: morphine combination. Our first formulation will be an oral tablet including a fixed-dose of pramipexole and one of at least two morphine doses. The morphine doses will be lower than are currently available in monotherapy tablets. Other combinations and methods of administration will be formulated and manufactured in collaboration with partners.

### Early development partnerships

Opioids drug products are administered in multiple formulations, depending on the clinical need. While oral doses are generally preferred, other methods of administration include intravenous, transdermal, sublingual, epidural, and intrathecal. Amalgent Therapeutics intends to develop oral doses for direct commercialization in the United States and work with partners for other geographies and methods of administration. For example, BioDelivery Sciences markets a transdermal formulation of buprenorphine for chronic use, this may be an attractive partner for U.S. commercialization of one or more transdermal applications of Amalgent's technology.

### Regulatory

On December 1<sup>st</sup>, 2022, Amalgent met with the FDA in a pre-submission meeting to discuss the pre-clinical and clinical pathway that AMGT-0220 will be able to follow. In this meeting, numerous risk-reducing elements of guidance were received as well as clarification on late-stage clinical requirements for AMGT-0220. Within the meeting a significantly positive event occurred when the FDA cleared the path to use pramipexole in our combined dose formulation for up to 6 times per day, thereby matching the frequency of acute pain treatment of administration every four hours. As a result, the dosing regimen will not require modifications from the current frequency when AMGT-0220 is used. The FDA provided insights on the pre-clinical pathway needed, which supports the Aims outlined in this proposal. As well, the FDA confirmed the use of the 505(b)2 pathway towards an NDA and clarified the basis of which formulation of opioid we may use as a precedent.

### Preparing the market for superior pain medications

During Phase 2 trials of our first combination, Amalgent Therapeutics will bring on a small commercial team to prepare a preliminary plan for product launch. After Phase 2 trials are completed in 2026, Amalgent will begin pre-approval activities in anticipation of a U.S. launch for the first combination. After the first NDA is submitted, a commercial organization will be built to support the specialty launch of the oral dose. The Company will collaborate with existing partners on the launch of other products based on the combination of opioids and dopamine 3 receptor agonists.

### Partners are collaborators, competitors, and acquirers.

Each of the firms noted in **Figure 7** and **Figure 8** are ideally suited to partner with Amalgent for development and launch of our products. While Amalgent will retain and develop oral doses of our combination medications,

the unmet need is greater than that and will lead to additional collaborations. Iconic examples would include Daichi-Sankyo and the BioDelivery Sciences example noted above.

Daichi-Sankyo is a global pharmaceutical company based in Japan. The company has a significant pain franchise that includes both opioid and non-opioid pain relievers. Given the company's reach and share (especially in Asia), Daichi-Sankyo would be an outstanding partner and/or acquirer.

**Patient Acquisition, Retention, and Growth.** The large number of patients in need gives rise to a significant opportunity for a multi-pronged rollout strategy, across geographies and acute patient settings. Educational acquisition efforts will include publication of research articles based on the results from our clinical initiatives. These will be authored by key opinion leaders in pain management.

Amalgent's primary focus will be the direct education of appropriate personnel in large medical centers via in-office visits, but will also include presentations at academic and medical conferences and the development of a medical science liaison team and patient and physician support/information lines to address any questions from the community. Networking, social media, online marketing, and public relations outreach to patient advocacy groups will also be integrated aspects of the marketing strategy. Amalgent will develop a patient financial assistance program that will help those with limited financial means to pay for the medication if they are not covered by appropriate insurance. With proven efficacy, patient word of mouth will be quite high by virtue of improvements in pain and reduced addictive effects. Growth of the market for Amalgent's product will be based on several factors including (i) acceptance in the broader medical community, (ii) expansion of the therapeutic indication to additional acute indications, (iii) healthcare economic data that influences payors to add Amalgent's product to formularies and (iv) the approval of Amalgent's product as a treatment in other geographies such as the E.U. by the EMA.

## Revenue Stream

As shown above, revenues for the next several years are projected to be up-front payments and milestones from partners. These partnerships will be driven by product development in ex-US geographies, and other than oral dose product development. Upon FDA approval, the Company's revenue stream will be of sales of pain medications.

General Revenue Estimates and Strategy—We will charge our pharma partners development fees, milestone fees, and royalties on sales for each product development project. The development fee consists of internal Amalgent costs, including fully loaded full-time equivalent (FTE) cost and cost of materials, as well as third-party cost, such as consultants, CRO, and CDMO cost. The development fee also includes a 5% mark-up over third party cost for managing and overseeing third-party activities. Total development per project cost can differ based on the type of product and the level of clinical improvement the pharma partner is seeking to achieve and validate in clinical studies. We expect total cost of development, sales, and marketing, to range from \$25 million to \$50 million per project, depending on the market and the partner's market capture target.

On top of the development cost, we will charge our pharma partners milestone fees, which reward us for achieving certain development milestones (e.g., successfully completing a feasibility study, filing an IND, filing an NDA, regulatory approval, etc.). Total milestone fees will differ per project, based on complexity and market size, and will range from ~\$5M-\$20M per project. In addition, once a product gets launched by our pharma partners, we will receive annual royalties on sales in the range of 5-10% of net sales.

We currently use a targeted, direct approach to reach our specialty pharma customers, who we identify based on internal market research, introductions by third parties, and one-on-one partnering possibilities at trade shows (e.g., BIO, Biotech Showcase). We qualify our leads through direct contact to establish whether they are interested in the type of products that we develop. After the qualification of leads, we will negotiate Development & License deals with the potential pharma partners. In most cases, these negotiations will be carried out with Business Development function of the Specialty Pharma partner. Most Specialty Pharma companies have a Business Development function, charged with scouting for new products to be in-licensed or acquired. This role is typically carried out by a

| Milestone payments             |                |
|--------------------------------|----------------|
| Up-front fee                   | \$10,000,000   |
| Initiation of clinical testing | \$500,000      |
| Completion of Clinical Testing | \$500,000      |
| Regulatory Approval (US)       | \$15,000,000   |
| 5% on Sales                    | >\$75,000,000  |
| <b>Total Revenues:</b>         | >\$103,000,000 |

*Figure 11. Typical structure of development & licensing*

Vice President or Director of Business Development, supported by other functions such as R&D, Legal, Manufacturing, and Regulatory Affairs. Usually, a company's CEO is involved in or oversees the final licensing or acquisition decision. Such deals include terms on development fees, milestone fees, and royalties on sales (to pay for the I.P. license that we provide our partners). Although the terms of individual Development & Licensing Agreements will vary, the typical structure of such an agreement, based on available databases of agreements with similar technologies and drugs, is detailed in **Figure 11**. We also expect to generate interest and create demand by presenting our scientific results at trade conferences, such as the International Association for the Study of Pain (IASP), National Conference on Pain Management, and by publishing favorable results on our innovation's achievements on our website and trade publications. In contrast to meetings such as BIO, where we market to business development professionals, forums such as IASP provide an ideal marketing opportunity to gain entry to customers from the R&D side of potential partner organizations. Event marketing at IASP, for example, will likely involve a greater emphasis on the presentation of scientific results via posters and seminars, as well as formal booths where we can present the scientific and clinical benefits of our technology to experts in the field who can influence product development decisions at their organization.

Revenue Projections for AMGT-0220 — Our first fixed-dose oral combination therapeutic is designated AMGT-0220. Using our co-development approach, we anticipate that a licensing agreement for AMGT-0220 would look much like **Figure 11** with milestone payments of ~\$10M (including approvals) and annual royalty payments of 5% on net sales (i.e., gross sales minus production and marketing costs). **Figure 12** provides projections on AMGT-0220 for the first four years following approval. Patent coverage is expected to extend through 2041. Assumptions include a) peak sales in 2033, declining over the remainder of patent life, b) market share of 10% per year, and c) production and marketing costs of up to 35% of gross sales for the co-development partner.

| Revenue            | Up to Approval      | 2030                 | 2031                 | 2032                 | 2033                 | 2034                 |
|--------------------|---------------------|----------------------|----------------------|----------------------|----------------------|----------------------|
| Milestone Payments | \$11,000,000        | \$15,000,000         | \$0                  | \$0                  | \$0                  | \$0                  |
| Revenue            | \$0                 | \$168,539,000        | \$413,192,000        | \$543,674,000        | \$554,548,000        | \$565,639,000        |
| <b>Total</b>       | <b>\$11,000,000</b> | <b>\$183,539,000</b> | <b>\$413,192,000</b> | <b>\$543,674,000</b> | <b>\$554,548,000</b> | <b>\$565,639,000</b> |

*Figure 12. Revenue Estimates for AMGT-0220 Co-development Milestones and Revenue (First 5 Years)*

## **COMPANY COMMERCIALIZATION HISTORY**

1. Amalgent Therapeutics, Inc was awarded Direct-to-Phase II SBIR on August 18, 2023 by the National Institute on Drug Abuse. The grant is 1R44DA059302-01 entitled "Development of an Opioid Sparing Therapeutic to Minimize Opioid Use Disorder and Tolerance in the Treatment of Pain." The total funding associated with this award is \$ 2,579,875. We have not reached commercialization yet but are continuing to move down that path. We are currently working on prototype batches of our formulation and performing GLP toxicity study to position us for IND submission.
2. We were recently awarded a Phase I SBIR grant on July 18, 2024 by the National Institute on Drug Abuse. The grant entitled "Mechanism and Efficacy of a Novel Opioid Adjuvant" (1R43DA059522-01) was for a total of \$220,668.

In the past five fiscal years, Amalgent Therapeutics, Inc. has not received more than 15 SBIR Phase II awards from the Federal Government.

## PHS 398 Cover Page Supplement

### 1. Vertebrate Animals Section

Are vertebrate animals euthanized?  Yes  No

If "Yes" to euthanasia

Is the method consistent with American Veterinary Medical Association (AVMA) guidelines?

Yes  No

If "No" to AVMA guidelines, describe method and provide scientific justification

.....

### 2. \*Program Income Section

\*Is program income anticipated during the periods for which the grant support is requested?

Yes  No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

\*Budget Period \*Anticipated Amount (\$) \*Source(s)

### 3. Human Embryonic Stem Cells Section

\*Does the proposed project involve human embryonic stem cells?  Yes  No

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: [http://grants.nih.gov/stem\\_cells/registry/current.htm](http://grants.nih.gov/stem_cells/registry/current.htm). Or, if a specific stem cell line cannot be referenced at this time, check the box indicating that one from the registry will be used:

Specific stem cell line cannot be referenced at this time. One from the registry will be used.

Cell Line(s) (Example: 0004):

### 4. Human Fetal Tissue Section

\*Does the proposed project involve human fetal tissue obtained from elective abortions?  Yes  No

If "yes" then provide the HFT Compliance Assurance

If "yes" then provide the HFT Sample IRB Consent Form

### 5. Inventions and Patents Section (Renewal applications)

\*Inventions and Patents:  Yes  No

If the answer is "Yes" then please answer the following:

\*Previously Reported:  Yes  No

### 6. Change of Investigator/Change of Institution Section

Change of Project Director/Principal Investigator

Name of former Project Director/Principal Investigator

Prefix:

\*First Name:

Middle Name:

\*Last Name:

Suffix:

Change of Grantee Institution

\*Name of former institution:

## PHS 398 Research Plan

|  |                                     |
|--|-------------------------------------|
| <b>Introduction</b>  |                                     |
| 1. Introduction to Application<br>(for Resubmission and Revision applications) |                                     |
| <b>Research Plan Section</b>   |                                     |
| 2. Specific Aims   | SA_AT_FT_2024.09.02_406PM.pdf       |
| 3. Research Strategy*  | RS_AT_FT_2024.09.02.pdf             |
| 4. Progress Report Publication List  |                                     |
| <b>Other Research Plan Section</b>   |                                     |
| 5. Vertebrate Animals  |                                     |
| 6. Select Agent Research   |                                     |
| 7. Multiple PD/PI Leadership Plan  |                                     |
| 8. Consortium/Contractual Arrangements   |                                     |
| 9. Letters of Support  | LOS_merged_AT_FT_2024.09.03.pdf     |
| 10. Resource Sharing Plan(s)   | RSP_AT_FT_2024.08.30.pdf            |
| 11. Other Plan(s)  | DMSP_AT_FT_2024.08.30.pdf           |
| 12. Authentication of Key Biological and/or Chemical Resources                 | Authentication_AT_FT_2024.08.31.pdf |
| <b>Appendix</b>  |                                     |
| 13. Appendix   |                                     |

**SPECIFIC AIMS** – *Amalent Therapeutics' is developing a first-in-class pain medication that reduces the risks of opioid use disorder (OUD) and opioid tolerance while maintaining unmatched opioid-mediated pain relief.*

The opioid crisis highlights the dangers of using opioids for managing moderate to severe pain, including the development of OUD, opioid tolerance, overdose, and death. Indeed, the number of annual opioid-related deaths in the U.S. in 2023 were estimated to be over 80,000.<sup>1</sup> Despite these risks, no alternative non-opioid medications have been approved by the Federal Drug Administration (FDA) that can fully replace opioids. The absence of alternative, equally effective pain management options underscores the critical need for innovative solutions that can reduce the dependence on high-dose opioid therapies without compromising analgesic efficacy.

Amalent Therapeutics is repurposing the FDA-approved Parkinson's disease drug pramipexole, a dopamine type 3 (D3) receptor agonist, to develop the first-in-class pain medication, AMGT-0220. Unlike current therapies, which either rely solely on high-dose opioids or non-opioid alternatives with limited efficacy, AMGT-0220 leverages the synergistic effects of pramipexole and low-dose morphine, a commonly used opioid, to maintain effective pain relief while significantly reducing the risk of OUD and opioid tolerance. Our comprehensive data package includes preclinical studies demonstrating 1) crosstalk between dopamine and opioid signaling pathways, 2) enhanced analgesic effects of morphine mediated by pramipexole in acute and chronic pain models, 3) mitigation of opioid-related reward-seeking behavior by pramipexole, and 4) prevention and mitigation of opioid tolerance by pramipexole in a neuropathic pain model.<sup>2-6</sup> Amalent holds a worldwide exclusive license for combining opioids and D3 receptor agonists for pain management and reducing or inhibiting opioid tolerance, addiction, and dependence (patent issued in 2021). The use of two FDA-approved drugs derisks the AMGT-0220 development program, positioning AMGT-0220 for rapid advancement through clinical trials and towards commercialization. At the pre-IND meeting, the FDA provided guidance on the clinical path for AMGT-0220. The goal of this Fast-Track SBIR project is to manufacture clinical batches of AMGT-0220, submit an IND application for AMGT-0220, and perform the first-in-human Phase 1 pharmacokinetic (PK) study in healthy volunteers. Amalent has assembled a team of experts in drug development, opioid pharmacology, pain management, IND submissions and regulatory affairs, and clinical trial design to successfully bring AMGT-0220 to the clinic. The specific aims for this Fast-Track are:

**Phase I – Aim 1: Manufacture clinical batches of AMGT-0220 drug product.** To provide sufficient doses of AMGT-0220 for clinical trials, we will prepare clinical batches of low-dose and high-dose AMGT-0220 using our established GMP manufacturing protocols and validated analysis methods. Milestones: Complete manufacturing of clinical batches; pass release criteria (Quantitative metrics: Manufacture 10,000 doses of low-dose and high-dose AMGT-0220 at >98% purity with individual impurities  $\leq$ 0.1%, meeting all release criteria).

**Aim 2: Submit an IND application for AMGT-0220.** In parallel to manufacturing of the AMGT-0220 clinical batch, we will prepare the IND package to be submitted at the end of this phase with the release of the clinical batch. The IND package will be prepared in partnership with Alluent, LLC. This aim will consist of preparing Modules 1–3, preparing eCTD-compliant nonclinical and clinical study reports for Modules 4 and 5, and submission of the IND application to the FDA. Milestones: Complete preparation of the IND package; submit IND application to FDA.

**Go/No Go for Phase II:** FDA receives IND package.

**Phase II – Aim 1: Conduct a Phase 1 open-label clinical trial in healthy volunteers.** Understanding the safety, PK, and relative bioavailability of AMGT-0220 is crucial for determining dosing regimens for future clinical trials. In this aim, we will conduct a randomized, crossover study in healthy volunteers (n=12; geometric least-squares mean ratio between 95% and 105%). Each participant will receive all treatments with a 3-day washout period between treatments. The treatments will consist of: A) AMGT-0220 (low dose – 0.125 mg pramipexole/7.5 mg morphine), B) AMGT-0220 (high dose – 0.125 mg pramipexole/15 mg morphine), C) morphine sulfate (15 mg, lowest available strength), D) pramipexole hydrochloride (0.125 mg). Blood samples will be collected at predefined intervals to measure pramipexole, morphine, and morphine metabolite plasma levels. Milestone: Determine bioequivalence and safety of AMGT-0220 in healthy volunteers (Quantitative/success metrics: 90% confidence intervals for the ratios of  $C_{max}$  and AUC between AMGT-0220 and reference drugs falls within 80% to 125%; no significant adverse events due to AMGT-0220).

Opioids continue to be the standard of care for moderate to severe pain, and the opioid market is expected to reach more than \$22 billion by 2026.<sup>7</sup> With no effective non-opioid drugs on the horizon, successful completion of this Fast-Track project will lay the foundation for subsequent Phase 2/3 studies and eventual NDA submission, ultimately bringing AMGT-0220 to the patients who need it most.

## SIGNIFICANCE

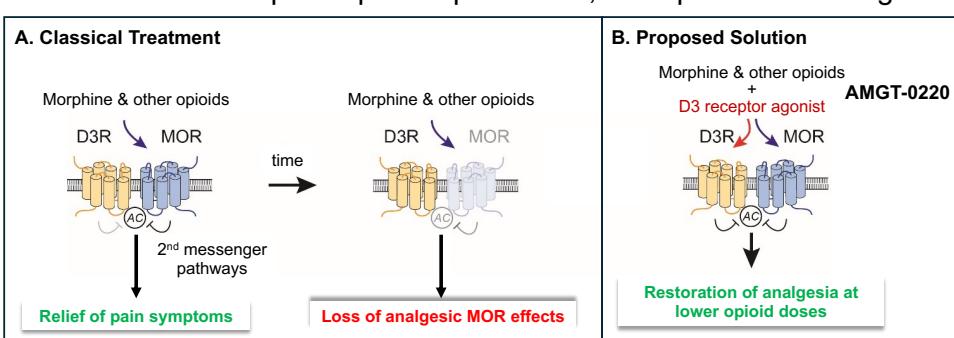
*Amalgent Therapeutics' is developing a first-in-class pain medication that reduces the risks of opioid use disorder (OUD) and opioid tolerance while maintaining unmatched opioid-mediated pain relief.*

**Problem:** *Opioids are the most effective pain relief for moderate to severe pain but come with high risks.* Opioids are highly effective analgesics and a critical therapeutic resource for treating moderate to severe pain.<sup>8</sup> They are used to treat pain related to oncology, surgery, and acute injuries (e.g., fractures, sprains, and burns) as well as chronic pain (e.g., osteoarthritis, back pain, and neuropathic pain) unmanaged by non-opioid medications.<sup>9</sup> More than half of the 18 million patients undergoing surgery each year receive postoperative opioids.<sup>10–12</sup> Although powerful pain medications, opioids have inherent risks to patients. They can cause respiratory depression, toxicity to the central nervous system, increased intracranial pressure, nausea, constipation, and hypotension. About 3–19% of patients prescribed an opioid will develop opioid use disorder (OUD), including dependence and addiction.<sup>13,14</sup> Over two million Americans have OUD,<sup>14</sup> and some will seek illicit opioids to deal with withdrawal and cravings. Despite decreases in opioid prescriptions, over 80,000 opioid-related deaths were estimated in 2022 and 2023.<sup>1</sup>

**Current non-opioid analgesics are insufficient for moderate to severe pain.** Despite the significant risks to opioid use, replacing opioids in pain management is challenging. A significant hurdle is the complexity of pain perception and modulation. Opioids exert their potent analgesic effects by binding to mu-opioid receptors in the central nervous system to effectively dampen pain signals; however, this signaling also activates the brain's reward pathways, leading to addiction. Non-opioid analgesics (e.g., nonsteroidal anti-inflammatory drugs and acetaminophen) lack the necessary potency to manage severe pain. Therefore, they cannot fully replace opioids. Advancements in molecular biology have steered research toward novel targets within pain pathways, which could help reduce the use of opioids but to date have failed to replace them fully. Vertex Pharmaceuticals' VX-548 is a selective inhibitor of the NaV1.8 sodium channel implicated in pain signaling. Despite the FDA's acceptance of its New Drug Application (NDA) in July 2024, VX-548 failed to replace opioid hydrocodone + acetaminophen in its Phase 3 clinical trial.<sup>15</sup> Zynrelef, a gel combination of anesthetic bupivacaine and NSAID meloxicam applied immediately post-surgery, was approved by the FDA in 2021. It has decreased opioid use by 18% in the 72 hours immediately following surgery,<sup>16</sup> however, most patients still required an opioid immediately after and in the days following surgery. Cannabinoid-based therapies, which target the endocannabinoid system, have potential analgesic properties without addiction risk; however, the clinical efficacy of cannabinoids for severe pain remains under debate, and their side effect profile, including psychoactive effects, poses additional challenges. Thus, despite intensive research, no non-opioid analgesics have been approved by the FDA for moderate to severe pain that can completely replace opioid use, leaving the core pain patients with only opioid-based drugs to effectively manage daily pain. **Therefore, therapeutic strategies that maximize the efficacy of opioids while significantly decreasing their risks are an urgent unmet need in pain management.**

*Amalgent Therapeutics is leveraging the interplay between opioid and dopamine receptor signaling to bridge the gap between opioid efficacy and safety to deliver effective pain management while mitigating the risks of developing OUD and opioid tolerance.* In the absence of a complete opioid replacement, attempts are still being made

to generate novel synthetic opioids with improved safety profiles. Methadone, introduced in the 1940s, offers extended pain relief but has a high propensity for dependence and intricate withdrawal symptoms. Buprenorphine, a partial opioid agonist produces less euphoria and respiratory depression but comes with the risks associated with misuse and addiction. Nektar Therapeutics' NKTR-181 was a novel opioid with slower central nervous system penetration expected to reduce opioid-related euphoria and abuse potential. It was abandoned in 2020 due to safety and efficacy concerns. The failures and risks of synthetic opioids and the



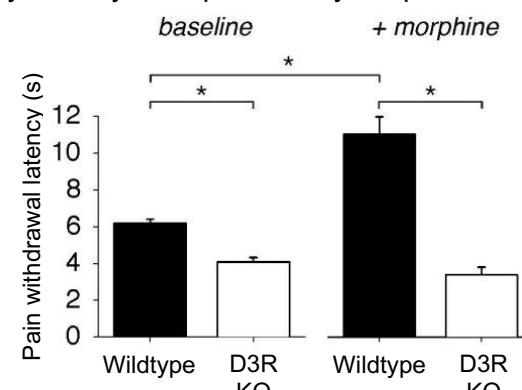
**Figure 1. Proposed interactions between D3R and MOR to alleviate pain.** **A.** With classical opioid analgesia, morphine and other opioids activate MOR to inhibit adenyl cyclase (AC) to block pain signaling (left). However, chronic activation of MOR leads to opioid tolerance, decreasing AC inhibition and reducing the analgesic effects of opioids (right). **B.** As D3R and MOR can form a heterodimer, a combination of D3R agonist and morphine as found in AMGT-0220 could potentially synergistically restore MOR-mediated AC inhibition, providing opioid-mediated analgesia at lower opioid doses.

lack of alternative non-opioid therapeutics to completely replace opioids underlies the critical need to find new solutions that make current, highly effective opioids safer and less addictive. One promising approach is the use of opioid adjuvants — drugs that enhance the analgesic effects of opioids while allowing for lower opioid dosages and reduction of the addiction potential, overdose, and tolerance. Adjuvants, such as gabapentinoids, antidepressants, or NMDA receptor antagonists, can modulate pain pathways in ways complementary to opioid action, potentially enhancing pain relief and reducing side effects. By targeting multiple pathways, these combinations can optimize pain management while minimizing the liabilities of high-dose opioid therapy.

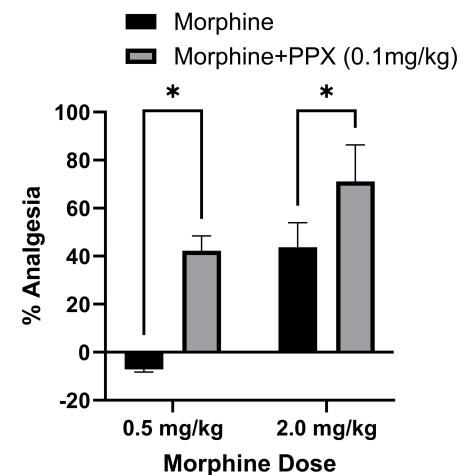
Amgent Therapeutics' AMGT-0220 is a novel therapeutic that combines pramipexole, a dopamine D3 receptor (D3R) agonist approved for Parkinson's disease and restless leg syndrome, and a subtherapeutic dose of morphine, a widely prescribed and gold standard in opioid pain treatment, in one tablet to provide a safer, synergistically enhanced opioid analgesic. Our preliminary animal and human data show that D3R agonism reduces the effective morphine dose by a minimum of four-fold while preventing OUD and tolerance.<sup>2-4,6,17</sup> Therefore, we can deliver superior pain relief compared to today's non-opioid medications at a fraction of the opioid doses currently used while blocking mechanisms leading to opioid tolerance and OUD. By combining two FDA-approved drugs into a novel formulation, we can expedite advancement through the 505(b)2 clinical path towards an NDA submission. If approved, this new therapeutic will change the opioid therapeutic landscape.

Scientific Premise: Interplay between opioid and dopamine signaling mediates the analgesic effects of opioids.

Opioid drugs, such as morphine, activate the opioid receptors, predominantly the mu-opioid receptor (MOR), which inhibits adenyl cyclase (AC) to reduce neurotransmitter release and block pain signaling in the central nervous system (Fig. 1A).<sup>18</sup> However, chronic or repeat activation of MOR leads to opioid tolerance in which higher and higher opioid doses are required to provide the same therapeutic effect due to desensitization of MOR signaling.<sup>19</sup> In the dorsal and ventral horns of the spinal cord, MOR co-localizes with D3R, even forming functional heterodimers in the latter.<sup>6,20</sup> As these horns are vital to modulating pain perception, the interplay between opioid and dopamine signaling is intricately involved in pain response (Fig. 1). Indeed, our published work has established the role of the D3R in morphine signaling and its necessity for morphine-mediated pain relief.<sup>2,3</sup> Using D3R knockout (KO) mice, we demonstrated that loss of D3R reduced the latency of withdrawal from a painful stimulus that could not be mitigated by morphine administration, i.e., morphine could not alleviate pain as it did in wildtype mice (Fig. 2). We observed a similar effect with excised spinal cords from wildtype and D3R KO mice, where morphine modulated spinal reflex amplitudes in WT cords but not in cords taken from D3R KO mice. Moreover, blocking the D3R with antagonist nafadotride in the isolated WT cord prevented morphine's inhibitory effects observed under control conditions. These data demonstrate a role for D3R in MOR signaling in the spinal cord. To further support this concept, we demonstrated that D3R signaling potentiated morphine-mediated analgesia in a rat tail-flick pain model in which a high-intensity light beam causes heat-induced pain, resulting in a flick of the rat's tail in response to the painful stimuli.<sup>21</sup> In this study, 0.5 mg/kg morphine (low-dose) provided no analgesia in contrast to 2 mg/kg (high-dose) (Fig. 3). Importantly, D3R agonism by pramipexole mediated analgesia by low-dose morphine to levels comparable to that of the high-dose and also provided additional analgesic effects for the high-dose treatment. Therefore, D3R activity plays a critical role in morphine-mediated pain relief. The collective data



**Figure 2. Loss of D3R prevents morphine-mediated pain relief.** The effect of D3R KO on morphine efficacy was determined using the Hargreave's test for thermal thresholds. Testing was performed before and after i.p. administration of 2 mg/kg morphine. Mice (n=15/group) received heat to a hind paw from an infrared light source through the glass floor of their compartment. The withdrawal latency was calculated (max 20 s). Each animal was tested 6 times/session (4 sessions). Data are presented as the mean pain  $\pm$  SEM ( $p<0.001$ ).



**Figure 3. D3R agonism potentiates morphine analgesia in rats.** Long-Evans rats (n=10) were administered low (0.5 mg/kg) or high (2 mg/kg) morphine in the absence or presence of 0.1 mg/kg pramipexole (PPX) and then subjected to the tail flick test. Data represent the mean percentage of analgesia relative to the control mice  $\pm$  SEM ( $p<0.05$ ).

provide a solid foundation for developing a pain therapeutic that combines a subtherapeutic dose of morphine with a D3R agonist, such as pramipexole.

***Rigor of the prior work.*** We have established the role of D3R in potentiating morphine analgesia in two independent models using both genetic knockout and chemical agonism of this important receptor. These statistically powered studies used two distinct pain models to establish the effects of D3R modulation on morphine-mediate pain relief, underlying the robustness of our studies. AMGT-0220 will contain fixed doses of pramipexole (0.125 mg) and doses of morphine lower than the standard doses when administered as monotherapy (3.75, 7.5 or 15 mg). Fixed-dose combinations in a single tablet are preferred by regulatory agencies and prescribers over the co-administration of two drugs for their simplicity and known safety profiles.<sup>22,23</sup> Further, a novel combination therapeutic formulation is warranted because oral opioids are currently not marketed at doses low enough to match dose levels in AMGT-0220 and other combinations in the pipeline. Pramipexole has been used for over 25 years in the clinic with little risk to patients.<sup>24-26</sup> The lowest available dose of PPX is 0.125 mg, taken three times per day. Patients are often titrated up to higher doses, with a maximum approved daily dose of 4.5 mg. The most commonly observed adverse effects (AEs) are somnolence and, to a lesser extent, the onset of impulse control disorders. Both of these AEs have only been observed at high pramipexole doses, not at low pramipexole doses ( $\leq 2$  mg/day).<sup>27,28</sup> Thus, there is a ~20-fold difference between the proposed doses in AMGT-0220 and that which could produce AEs, indicating a wide safety margin for AMGT-0220. This safety margin is supported by a lack of label contraindications for pramipexole for patients taking opioids, and Parkinson's patients taking dopamine agonists are routinely prescribed opioids for pain. The effect of pramipexole on addiction is an essential consideration for our technology. Published studies show that the D3R antagonist VK4-116 at 5 mg/kg attenuates oxycodone self-administration and reinstatement addiction in mice.<sup>29</sup> This result raises the question of whether pramipexole, a D3R agonist, could increase the potential for opioid addiction. Our results have demonstrated the opposite is true as 0.1 mg/kg pramipexole decreased morphine reward potential in rats (see **Preliminary studies in Approach**).<sup>4</sup> Moreover, chemical inhibition (antagonist SCH 39166) of the dopamine D1 receptor (D1R), which has opposite downstream effects on adenylyl cyclase and protein kinase A activity to D3R, replicated the effects of pramipexole on morphine preference, prevention of tolerance, and withdrawal.<sup>4-6</sup>

Because AMGT-0220 will combine two FDA-approved drugs in one therapeutic, safety risks have been reduced. Neither drug is expected to have a significant impact on the other's pharmacokinetics (PK) profile as they do not interact with the same receptors in the central nervous system.<sup>30,31</sup> Although at high doses, pramipexole inhibits CYP enzymes, morphine is not degraded by this mechanism, and the dose of pramipexole in AMGT-0220 is low. This risk is also being mitigated by the Phase 1 PK study in healthy volunteers proposed in Phase II Aim 1 of this SBIR Fast-Track. Furthermore, available repeated-dose studies in animals and clinical data on the individual drugs indicate that there is little overlap in target organs and toxicities.

***Health impact.*** Millions of individuals suffer from acute or chronic pain. Unlike current therapies, which either rely solely on high-dose opioids or non-opioid alternatives with limited efficacy, AMGT-0220 leverages the synergistic effects of pramipexole and a low-dose opioid to maintain effective pain relief while significantly reducing the risk of OUD and opioid tolerance. Therefore, AMGT-0220 will likely replace current opioid monotherapy to offer safer, effective treatment for moderate to severe pain.

***Strength of the Amalgent team.*** Amalgent Therapeutics, Inc., is an early-stage drug development company based in North Carolina. The company is led and supported by a team with extensive experience in drug development and pain pharmacology. **Malcolm Meyn, PhD, MSHS** (Project PI, CSO, Amalgent), has extensive drug development experience, including directing research and development projects in regulated and non-regulated environments. He has experience managing CROs and other vendor contracts and has contributed to multiple pre-IND and IND submissions. He also has training in managing biotechnology projects, regulatory strategy, and clinical trial design. **Sam Tetlow, MBA** (President, Amalgent) is an experienced life sciences entrepreneur and led Amalgent's efforts to raise \$1,000,000 in private funding. **Frank Porreca, PhD** (Pharmacology Advisor, SAB Member), Associate Department Head of Pharmacology at the University of Arizona, is an internationally recognized expert in opioid pharmacology and pain research. **Gerald Klein, MD** (Chief Medical Officer, Amalgent) is an accomplished expert in pain therapeutic drug development, with roles as Chief Medical Officer at Oxygen Biotherapeutics, Talecris/Grifols, and Entera Health. Dr. Klein's leadership in clinical trials and medical affairs has been pivotal in advancing pain management therapies in the field and is well suited to advance AMGT-0220. **Charles Argoff, MD** (Key Opinion Leader, SAB Member) is a Professor of Neurology and Director of the Comprehensive Pain Program at Albany Medical Center. As a luminary in the field of pain management, he has consulted with leading firms in the field and remains a key opinion leader in the domain of leading pain

management. He advises Amalgent on clinical strategy and product label design. **Gillian Schmitz, MD** (Emergency Medicine advisor, SAB Member) is a board-certified emergency physician, an Associate Professor at the Military and Emergency Medicine Uniformed Services University of the Health Sciences, and Vice Chair of Education Brooke Army Medical Center. She advises Amalgent on emergency medicine aspects of pain management. **Peter Barton Hutt** (SAB Member) is the former chief counsel for the FDA and is currently a senior attorney at Covington & Burling LLP, specializing in Food and Drug Law. He helped draft legislation to create the National Institute of Alcohol Abuse and Alcoholism and the National Institute of Drug Abuse. **Allucent** (Medical and Regulatory Consulting) is a regulatory consulting firm with over 30 years of experience as a global provider to drug developers, including regulatory affairs consulting and services to small and midsize biotechnology companies.

## INNOVATION

Amalgent Therapeutics has established a worldwide exclusive license for the combination of D3R agonists with opioids for moderate to severe pain indications. Lead AMGT-0220 combines fixed low doses of pramipexole and morphine, a staple in post-surgical pain management. The innovations behind AMGT-0220 that differentiate it from current approaches to pain medications (**Table 1**) include:

- **Novel combination pain medication.** AMGT-0220 combines two FDA-approved agents with established safety profiles from long clinical histories. The repurposing of the Parkinson's drug pramipexole for pain management to enhance morphine efficacy provides a unique opportunity to lower opioid doses without affecting pain relief, a current challenge in the field.
- **Mitigating the risk of OUD and opioid tolerance without reducing potency.** AMGT-0220 differentiates itself from current opioid, non-opioid, and alternative therapy approaches (**Table 1**). It is a first-in-class combination pain medication that allows a reduction in morphine dose without loss of therapeutic potency while preventing the development of opioid tolerance or OUD.

To date, there are no non-opioid therapeutics approved or in the pipeline that can fully replace opioids for the management of moderate or severe pain. While some, such as Zynrelef and VX-548, can help reduce the number of opioid prescriptions, their effectiveness is dependent on the case and neither could fully substitute for opioids. Therefore, opioids continue to be the mainstay for effective pain management. The ability

to reduce opioid dose and inherent risks without affecting the superior analgesia provided by opioids gives AMGT-0220 a significant advantage over current therapeutic approaches for pain.

**Intellectual property (IP) protection.** Amalgent holds a worldwide exclusive license to inventions made by Kori Brewer, Ph.D. and Stefan Clemens, PhD. of East Carolina University. We have two published US patents: 1) treatment of pain; 2) prevention of addiction. A third patent for the prevention of opioid tolerance has been filed. Patents are also actively being pursued in Canada and Europe.

**Path to commercialization.** The commercialization pathway for AMGT-0220, including the position of the SBIR Fast-Track in the path, is presented in **Fig. 4**. Amalgent has already had a Pre-IND meeting with the FDA to discuss the clinical development of AMGT-0220. We received guidance on our clinical path for the development of AMGT-0220, and the agency confirmed that AMGT-0220 would be regulated as a 505(b)2 product, which will allow us to use the safety data from each of the individual reference molecules and will significantly decrease regulatory risk for this first therapeutic. The Target Product Profile for AMGT-0220 in comparison to reference compounds morphine and pramipexole are presented in **Table 2**. We aim to get approval for AMGT-0220 containing 7.5 mg morphine first and then proceed to the lower dose of 3.75 mg. In addition, we received guidance

| Characteristic                 | Current Opioids <sup>a</sup> | Current non-opioid pain medications <sup>b</sup> | Alternative approaches <sup>c</sup> | AMGT-0220 |
|--------------------------------|------------------------------|--|-------------------------------------|-----------|
| Manage acute pain              | YES                          | YES/NO <sup>d</sup>                              | NO                                  | YES       |
| Manage chronic pain            | YES                          | YES/NO <sup>d</sup>                              | YES/NO <sup>d</sup>                 | YES       |
| Manage moderate pain           | YES                          | YES/NO <sup>d</sup>                              | YES/NO <sup>d</sup>                 | YES       |
| Manage severe pain             | YES                          | NO   | NO                                  | YES       |
| Significant side effects       | YES                          | YES/NO <sup>d</sup>                              | NO                                  | NO        |
| Potential organ toxicity       | YES/NO <sup>d</sup>          | YES  | NO                                  | NO        |
| Abuse potential                | YES                          | NO   | NO                                  | NO        |
| Dependence/addiction potential | YES                          | NO   | NO                                  | NO        |

<sup>a</sup>Current opioid pain medications include codeine, morphine, oxycodone, fentanyl

<sup>b</sup>Current non-opioid pain medications include ibuprofen, acetaminophen, naproxen, Zynrelef, VX-548

<sup>c</sup>Alternative approaches include acupuncture, psychological and physical therapy, injections, and medical devices

<sup>d</sup>Yes/No, depends on case, severity of the illness/injury, and pain threshold

on preclinical safety studies, reference drugs, and potential safety claims for the marketed product. The Agency emphasized that safety concerns for the inclusion of pramipexole are minimal at our proposed doses. We will continue to confer with the FDA on AMGT-0220 throughout its development with ad hoc meetings. We are currently manufacturing a prototype AMGT-0220 batch and completing PK and GLP safety studies through private investment (\$1 million) and a NIDA Phase 2 SBIR Award (DA059302). This SBIR Fast-Track will be essential for obtaining FDA clearance to proceed with clinical studies and carry out the IND opening Phase 1 PK study in healthy volunteers. Following the Phase 1 PK study, we will proceed with additional Phase 1 studies, Phase 1/2, and pivotal Phase 3 studies in addition to a human abuse liability study. Clinical demonstration of AMGT-0220 efficacy against moderate to severe pain that is equal to or better than current opioid medications at a fraction of the dose and without the risks of opioid tolerance or dependence will position AMGT-220 to replace current opioid monotherapy treatment (see **Commercialization Plan** for details).



**Figure 4. Positioning of the Direct-to-Phase II SBIR in the commercialization pathway.**

**Table 2: Target Product Profile for AMGT-0220**

| <b>Description</b>      | <b>Target Product Characteristics</b>  | <b>Reference Morphine Drug</b>  |
|-------------------------|--|---|
| <b>Therapeutic Area</b> | Moderate to severe pain  | Moderate to severe pain   |
| <b>Population</b>       | Adults with pain where the use of an opioid analgesic is appropriate and not treatable by non-opioid methods | Relief of moderate to severe acute and chronic pain where the use of an opioid analgesic is appropriate |
| <b>Dosage Form</b>      | Oral bilayer tablet, abuse deterrent formulation   | Oral tablet   |
| <b>Daily Dosage</b>     | Every 4 hours as needed  | Every 4 hours as needed   |
| <b>API</b>              | 0.125 mg PPX: 15 mg morphine<br>0.125 mg PPX: 7.5 mg morphine<br>0.125 mg PPX: 3.75 morphine                 | 15 mg morphine<br>30 mg morphine  |

## APPROACH

### Preliminary data

The published and unpublished data presented in the **Significance** section and in this **Preliminary data** provide a solid foundation for combining pramipexole with morphine as an effective therapeutic for management of moderate to severe pain that would otherwise be treated with an opioid monotherapy. We demonstrated that pramipexole reduces the dose of morphine required for analgesia in animal studies and in a human clinical study. Our published data demonstrate that pramipexole ameliorates morphine reward potential,<sup>4</sup> increases morphine efficacy against neuropathic pain,<sup>4</sup> prevents opioid tolerance and restores opioid efficacy in opioid tolerant animals,<sup>6</sup> and minimizes withdrawal symptoms following cessation of opioid administration.<sup>6</sup> Select preliminary data is presented below.

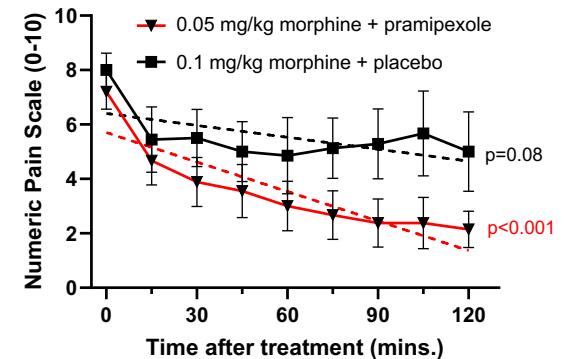
**Pramipexole increases morphine efficacy in animal and human studies.** As described in the significance section, the combination of 0.1 mg/kg pramipexole to a sub-therapeutic dose of morphine (0.5 mg/kg) produced comparable efficacy to the high therapeutic dose of 2 mg/kg morphine monotherapy in the rat tail-flick model of acute pain (**Fig. 3**). Administration of PPX in combination with 0.5 mg/kg morphine restored analgesia at this dose to levels nearly equal to that of 2.0 mg/kg morphine monotherapy. Moreover, in an investigator-initiated double-blinded, placebo controlled randomized trial at East Carolina University (NCT0416052), the combination of lower dose morphine (0.05 mg/kg, i.v.) and pramipexole (0.25 mg, p.o.) (n=10) were compared to standard of care morphine monotherapy (0.1 mg/kg, i.v. + placebo pill) (n=9) for treatment of acute renal colic pain not relieved with nonsteroidal anti-inflammatories. Pain scores were obtained prior to administration of study drugs and at 15-minute intervals ( $\pm$  2 min) after treatment for up to 2 h or discharge. In this pilot study, 80% of patients receiving morphine + pramipexole had effective analgesia by the end of the study period compared to only 33.3% in the higher dose morphine only arm (**Fig. 5**) (in press). Indeed, the analgesia provided by low-dose morphine + pramipexole continued to increase beyond 15 min, whereas standard of care plateaued, indicating the potential for combining lower dose morphine with pramipexole for severe acute pain.

**Pramipexole decreases the addictive potential of morphine.** To determine the effects of pramipexole on the rewarding effects of morphine, a conditioned place preference (CPP) study was performed.<sup>5</sup> Pramipexole (0.1

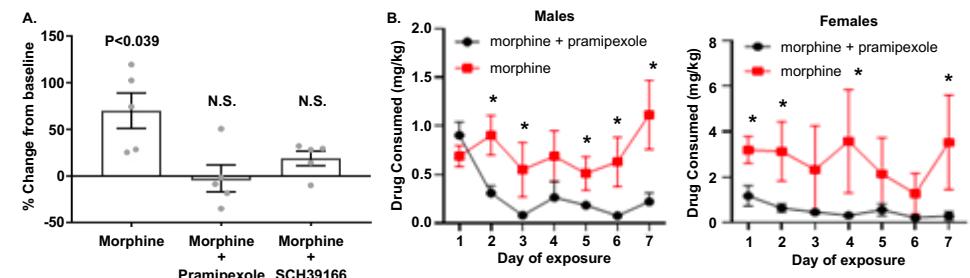
mg/kg) reduced the reward potential of 2 mg/kg morphine (**Fig. 6A**). Similarly, the dopamine D1 receptor antagonist SCH39166 reduced morphine reward potential. Since D1R and D3R have opposite effects on dopaminergic signaling, the similar effects of the D3R agonist and D1R antagonist provides further support that pramipexole is acting through D3R and not through off-target activation of other receptors and underlines the potential of modulating dopaminergic signaling for controlling the addiction potential of opioids. In an independent test of the effect of pramipexole on the addiction potential of morphine, we used the 2-bottle choice test in rats (**Fig. 6B**). In this test, rats are given free access to two bottles (test article vs. vehicle) and the consumption from each bottle is measured for 7 days. Preference for test article over vehicle indicates addiction potential. In our study, we compared the preference of male and female rats for morphine in 3% sucrose or morphine + pramipexole in 3% sucrose vs. 3% sucrose vehicle. The test solutions were prepared in sucrose to prevent the test of the drugs from influencing consumption. In both male and female rats, there was a preference for morphine over vehicle. In contrast, consumption of morphine + pramipexole decreased over time, indicating that the D3R agonist reduced the addiction potential of morphine.

**Pramipexole prevents opioid tolerance and withdrawal.** The effect of pramipexol on the development of morphine tolerance was tested in rats using the tail flick test<sup>6</sup> (**Fig. 7**). Rats were chronically administered saline (**A**), morphine (**B**), morphine + pramipexole (**C**), or morphine + SCH39166 (**D**) for 14 days by osmotic pump. The analgesic effects of an acute 2 mg/kg morphine injection were tested in these chronically treated rats on days 7 and 14 post-pump implantation using the tail flick test. Chronic administration of morphine alone, but not saline or morphine combined with pramipexole or SCH39166 (D1 receptor antagonist), reduced the analgesic effects of acute morphine treatment. These data demonstrated that pramipexole and SCH39166 prevented the development of morphine tolerance. In the same study, pramipexole and SCH39166 decreased the duration of morphine withdrawal symptoms.<sup>6</sup> Consistent with these results, a case study by Sakurai et al.<sup>32</sup> showed that pramipexole relieved the withdrawal symptoms of the opioid oxycodone, further demonstrating that pramipexole could improve OUD-related conditions.

**CMC for AMGT-0220 is ongoing.** In the context of our current Direct-to-Phase II SBIR funding, we are performing key CMC and GLP toxicity testing. Amalgent has contracted Catalent Pharmaceutics to complete development and manufacture of AMGT-0220. They have completed method development for content uniformity, dissolution, and Karl Fisher water determination, and assay and related substances methods. They have achieved impurity resolution appropriate for ICH compliance for a Phase 1 development project and are finishing method qualification. They have also completed an excipient compatibility study to support formulation development and produced ten 50g lab scale non-GMP development batches for selection of an optimal formulation. From the ten



**Figure 5. The combination of pramipexole and low-dose morphine provides better analgesia than standard of care morphine in renal colic patients.** Pain ratings over time using the 0-10 Numeric Pain Scale. Dotted lines represent predicted slope based on a mixed linear model of change in score within each group over time. Data are presented as the mean  $\pm$  SEM. Groups had similar pain ratings prior to treatment and showed a similar decrease at 15 minutes after treatment. Beyond 15 minutes, pain ratings for patients receiving pramipexole + low-dose morphine continued to decrease while those receiving standard-of-care morphine remained constant. p-values = significance of predicted slope.



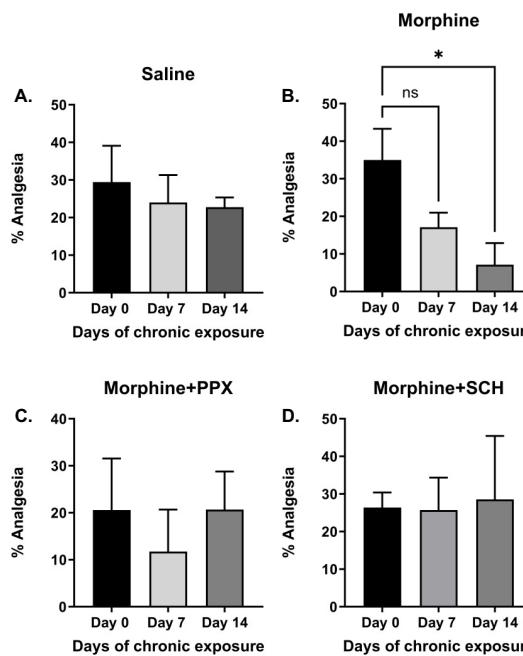
**Figure 6. Pramipexole reduces the addiction potential of morphine in two independent rat models.** **A.** The conditioned place preference test was performed in a three-chambered conditioned place preference apparatus.<sup>5</sup> After establishing the baseline, the rats were randomly assigned to a treatment group (2 mg/kg morphine only, 2 mg/kg morphine + 0.1 mg/kg pramipexole, or 2 mg/kg morphine + 0.1 mg/kg SCH 39166) and conditioned over a 7-day period. Following injection, the rats (n=5/group) were restricted to the designated chamber for 30 min. The rats were tested for place preference 24 h after the last conditioning session for 20 min. The amount of time spent in each chamber was determined. **B.** The 2-bottle choice test consisted of the following groups: 1) morphine in 3% sucrose (65.8  $\mu$ M) vs. 3% sucrose (n=6/sex); 2) morphine (65.8  $\mu$ M) + pramipexole (2.8  $\mu$ M) in 3% sucrose vs. 3% sucrose (n=10/sex). For each group, male (left) and female (right) rats were given free access to the two different solution-filled bottles. The consumption of each solution was monitored for 7 days. Data for both studies are presented as the mean  $\pm$  SEM (\*P<0.05).

formulations, two lab batches were scaled to 400 g and no stability issues were observed at 3 months. Catalent is currently working on full scale GMP prototype batches, with six month stability samples expected in Q1 2025.

## Phase I

### Aim 1: Manufacture clinical batches of AMGT-0220 drug product.

**Rationale:** To provide sufficient doses of AMGT-0220 for clinical trials, we will prepare clinical batches of low-dose and high-dose AMGT-0220 using our established GMP manufacturing protocols and validated analysis methods. Our Target Product Profile, as discussed with the FDA, is an oral tablet to be taken six times a day that contains 0.125 mg immediate-release pramipexole combined with 3.75 mg, 7.5 mg, or 15 mg immediate release morphine. For the Phase I study, we will evaluate fixed-dose combination tablets with 7.5 and 15 mg immediate-release morphine. The high morphine dose of 15 mg reflects the lowest morphine dose available by prescription. The milestones and success metrics for this aim are provided in **Table 3**.



**Figure 7. Pramipexole prevents opioid tolerance and withdrawal.<sup>6</sup>** The effects of chronic treatments on pain relief were determined using the rat tail flick assay as described in the **Significance**. **A.** Chronic infusion of saline by osmotic pump did not alter the analgesic effects of an acute morphine injection (2 mg/kg) 7 or 14 days after pump implantation. **B.** Chronic morphine infusion significantly decreased the analgesic effects of acute morphine injection 14 days after pump implantation relative to day 0. **C.** Chronic infusion of morphine in the presence of pramipexole did not have an effect on acute morphine analgesia 7 or 14 days after pump implantation compared to day 0. **D.** Chronic infusion of morphine in the presence of SCH (SCH 39166) did not affect the analgesic effects of an acute morphine injection, 7 or 14 days post-pump implantation compared to Day 0. Data are presented as the mean  $\pm$  SEM (n=35, \*p < 0.05 vs. 0 h).

**Table 3: Phase I, Aim 1 Milestones**

| Milestone                                     | Analysis Method  | CRO                     | Success/Quantitative Metric  |
|---|--|-------------------------|--|
| 1.1 Manufacture clinical batches of AMGT-0220 | LC-MS/MS, HPLC   | Catalent BioPharma, LLC | 10,000 doses of low-dose and high-dose AMGT-0220 at >98% purity with individual impurities $\leq$ 0.1% |
| 1.2 Analysis for clinical release             | microbial limit testing (sterility), color (appearance), NMR/MS (identity), HPLC (purity), gas chromatography (residual solvents), and Karl Fischer titration (moisture) | Catalent BioPharma, LLC | Meets 100% of release criteria   |

**Milestone 1.1 Manufacture clinical batches of AMGT-0220.** GMP-grade pramipexole has been purchased from Curia Global, and GMP-grade morphine has been obtained from Noramco. Clinical batch AMGT-0220 will be prepared by Catalent Pharmaceuticals in a GMP facility using methods and a formulation strategy validated with the GMP prototype batch. To generate fixed-dose combination tablets containing 0.125 mg pramipexole + 7.5 mg morphine or 0.125 mg pramipexole + 15 mg morphine, pramipexole and morphine are combined at the indicated doses into immediate release formulations that match the release kinetics of their respective reference drugs. This formulation strategy is well-established and has been successfully used in multiple FDA-approved combination therapeutics. The clinical batch will be 500 g in size, providing sufficient product for analysis and clinical use.

**Milestone 1.2 Analysis of clinical batch for release.** The work centered around CMC, GMP manufacturing and scale up, and development and validation of analytical methods has been and continues to be performed under a separate Direct-to-Phase II SBIR award to Amalgent. Using the validated analytical methods, we will perform hazard evaluation according to ICH/FDA Quality Risk Management Q9(R1) guidelines.<sup>34,35</sup> Analysis will include yield, and purity (HPLC), identity (NMR/MS), color (appearance), gas chromatography (residual solvents), Karl Fischer titration (moisture), and microbial limit testing. These methods have already been developed and validated under the current contract with Catalent.

**Expected outcomes, pitfalls, and alternative approaches.** To mitigate risk in manufacturing the complex oral formulation of AMGT-0220, Amalgent has enlisted Catalent Pharmaceuticals, a CDMO that specializes in innovative complex formulations. Therefore, we expect to have the target quantity of AMGT-0220 tablets manufactured at the target purity. Prior to the manufacture of this clinical batch, our formulation will be validated in a GMP prototype batch. Catalent has already completed formulation and process development as well as method development for the analytical methods and is currently validating these processes and methods under our existing Direct-to-Phase II grant. This minimizes risks to the clinical batch. Potential pitfalls include lower dosage than expected for either reference drug or drug release characteristics that do not meet the target product profile. If this is the case, Catalent will perform root cause analysis to identify and address these issues, including additional optimization of the formulation and GMP manufacturing process.

### **Aim 2: Submit an IND application for AMGT-0220.**

**Rationale:** To initiate clinical development of AMGT-0220, regulatory approval via an IND application is critical. Therefore, in parallel with manufacturing the clinical AMGT-0220 batch, we will prepare all the necessary documents and reports needed to support the IND application. This will enable us to submit the IND after completion of Aim 1 and the release of the clinical material. IND applications consist of five modules: Module 1 – Administrative Information and Prescribing Information; Module 2 – Summary Information; Module 3 – Quality; Module 4 – Nonclinical Study Reports; Module 5 – Clinical Study Reports. We will partner with Allucent, LLC (Cary, NC) to compile the IND package and submit to the FDA. Allucent is a clinical research organization with over 30 years of experience as a global provider of drug development, including regulatory affairs consulting and services to small and midsize biotechnology companies. Amalgent Therapeutics will transfer all materials needed to prepare the IND package to Allucent. The milestones and success metrics for this Phase I aim are provided in **Table 4**.

| <b>Table 4: Phase I, Aim 2 Milestones</b>   |                          |   |
|---|--------------------------|---|
| <b>Milestone</b>  | <b>Responsible Party</b> | <b>Success Metric</b>   |
| 2.1 Prepare eCTD compliant nonclinical and clinical study reports for Modules 4 and 5 | Allucent                 | Modules 4 and 5 completed according to the agreed upon timeline.  |
| 2.2 Complete preparation of Modules 1–3 of the IND package                            | Allucent                 | All materials transferred to Allucent according to the agreed upon timeline.<br>Modules 1–3 finalized and approved by both parties. |
| 2.3 Submit IND application to the FDA   | Allucent                 | Complete IND package compiled.<br>IND filed according to the agreed upon timeline.  |

**Milestone 2.1 Prepare eCTD compliant nonclinical and clinical study reports for Modules 4 and 5.** Because many aspects of Modules 1–3 rely on data and information from the studies performed to support the IND, we will initiate the compiling of the nonclinical and clinical study reports for Modules 4 and 5, respectively, before the first three modules. Reports for nonclinical studies not performed at contract research organizations will be drafted by Allucent in a format compliant with eCTD requirements.

**Milestone 2.2 Complete preparation of Modules 1–3 of the IND package.** Allucent will draft Modules 1–3 from the materials provided by Amalgent. They will also provide the guidance and drafting of a full clinical protocol and the Investigators Brochure. The requirements for each module are detailed below:

**Module 1** will include: 1) a cover letter with all pertinent company information and a brief summary of the submission; 2) Table of Contents; 3) Form FDA 1571, covering relevant certifications and agreements; 4) Form FDA 3674, certifying compliance with requirements for clinical trial registration; 5) General Investigational Plan, which provides an overview of the planned investigation (i.e., study purpose, rationale, subject population, and timelines); 6) Investigator's Brochure, which provides all the information about the drug (e.g., how it works, studies done on the product, clinical and nonclinical data, potential side effects); 7) Detailed clinical study protocols for studies to be conducted under the IND; 8) Information about the use of the drug, including labeling materials.

**Module 2** will consist of a brief overview of AMGT-0220 and the IND package, summaries of non-clinical studies (pharmacology, pharmacokinetics, and toxicology data) and clinical information (any human studies, including effects, and proposed mechanism(s) of action), and a synopsis for Modules 4 and 5. Because clinical development of AMGT-0220 is following the 505(b)2 path, the compiled data will focus on presenting our case for the safety of our fixed dose combination drug.

**Module 3** will include all Chemistry, Manufacturing, and Control (CMC) Information, including all technical information related to AMGT-0220's formulation, manufacturing, stability, packaging, and labeling. The completed modules will be reviewed and approved by Amalgent prior to final compilation of the IND package.

**Milestone 2.3 Submit IND application to the FDA.** After review and approval of the finalized Module 1–3 documents by Amalgent, Allucent will assemble the IND package and submit the application to the FDA on Amalgent's behalf.

**Expected outcomes, pitfalls, and alternative approaches.** We currently have all the materials needed to generate all documents required for the different modules and, therefore, do not expect any issues with compiling a complete IND package. It is possible that the compilation of nonclinical reports, particularly those for studies not carried out by contract research organizations, may take longer to complete. If this appears to be the case, we will expedite the process by expanding our writing team. It is unlikely that the FDA will not accept the IND after initial submission based on the Pre-IND meeting and our compliance with all FDA requests. During the Pre-IND meeting, the FDA agreed that the IND opening study would be a PK study. Reasons for a potential clinical hold could be the clinical trial design or safety concerns. If this is the case, we will have an additional meeting(s) with the FDA to develop the best course of action to address their concerns and execute the plan, including completing any requested safety studies, to move the project forward to acceptance and initiation of the trial.

**Go/No Go for Phase II:** FDA receives IND package.

## Phase II

### Aim 1: Conduct a Phase 1 single-dose PK clinical trial in healthy volunteers.

**Rationale:** Understanding the PK of AMGT-0220 is crucial for determining its safety, efficacy and optimal dosing regimen for future clinical trials. For a drug that combines two active ingredients, it is important to determine whether each component affects the PK, metabolism, and clearance of the other. To this end, we will perform a Phase I open-label study in healthy volunteers to evaluate the safety pharmacokinetics

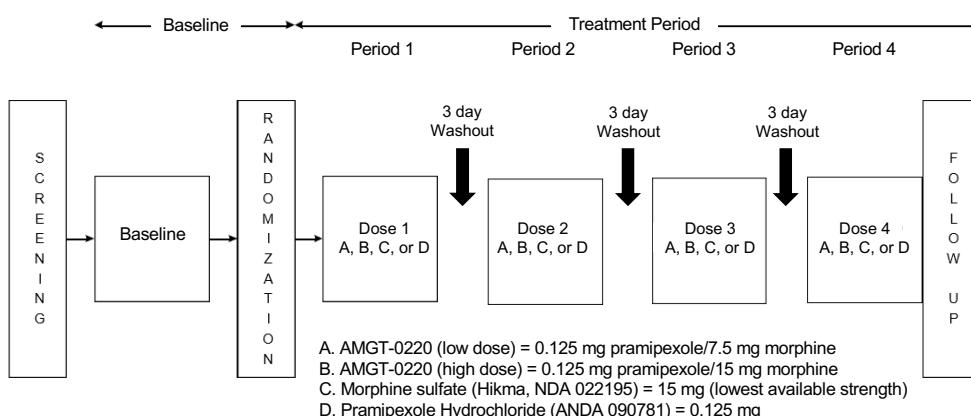


Figure 8. Study design for the Phase I open-label trial in healthy volunteers.

and relative bioavailability of AMG T-0220 at low and high dose levels compared to morphine and pramipexole administration alone. The study will consist of 12 healthy volunteers, who will be administered each treatment using a randomized 4-way crossover design. **Scientific rigor:** Sample size was determined by assessing the published pK values and variability for pramipexole and morphine.<sup>36</sup> Power analysis (80%) was conducted independently for both Cmax and AUC to determine the number of participants needed to meet the study's objectives. Based on Cmax, the required sample size is 5 participants, with an expected standard deviation of 2.7 ng/mL. From calculations based on AUC, the sample size is 4 participants (standard deviation of 13.5 ng·h/mL). Since the sample size must be adequate for both primary endpoints, the larger sample size of 5 participants is needed to ensure the study is adequately powered. An equal number of males and females will be enrolled to address sex as a biological variable. To account for potential patient dropout, six males and six females will be recruited. We will evaluate the levels of these two drugs along with the two major metabolites of morphine (morphine-3-glucuronide, morphine-6-glucuronide) generated in humans. This study will be performed and managed through PPD, a leading CRO with over 30 years of experience conducting and managing clinical trials, including sample analysis. They have supported over 1,600 clinical trials and projects for the U.S. government, and have 70+ active contracts for NIH, BARDA, CDC, DoD, non-profits, and academia partners. The study will adhere to the

Table 5: Phase II, Aim 1 Milestones

| Milestone   | Analysis Method   | CRO | Quantitative/Success Metric  |
|---|---|-----|--|
| 1.1 Bioanalytical development and validation  | LC/MS/MS  | PPD | calibration range, assay precision and accuracy  |
| 1.2 Determine the PK profile and safety/tolerability of AMGT-0220 in healthy volunteers | Noncompartmental analysis<br><br>12-lead electrocardiograms (ECGs), vital signs, pulse oximetry, clinical laboratory tests, and physical examinations | PPD | 90% confidence intervals for the ratios of Cmax and AUC between AMGT-0220 and reference drugs falls within 80% to 125%<br><br>no significant adverse events from AMGT-0220 |

Declaration of Helsinki, Good Clinical Practices, and all applicable regulatory requirements. The study will be performed under an IRB-approved protocol. The milestone and success metrics for this aim are in **Table 5**.

**Milestone 1.1 Development and validation of bioanalytical methods.** Morphine and pramipexole levels will be measured in the plasma of healthy volunteers. Therefore, we will develop robust bioanalytical methods for this assessment. A morphine LC-MS/MS method is already established. Here, we will develop a LC/MS/MS assay for the determination of pramipexole in human plasma containing K2EDTA from a target volume of 100  $\mu$ L, establishing the calibration range, assay precision, and accuracy. We will then validate the assay, including sample stability up to one month. We will also determine the potential interference of pramipexole detection by morphine and its metabolites.

**Milestone 1.2 Determine the PK profile and safety/tolerability of AMGT-0220 in healthy volunteers.** The schema for the proposed Phase 1 open-label study in healthy volunteers is presented in **Fig. 8**.

**Study design.** The study will be a Phase 1, randomized, open-label, four-period, single-dose, crossover study in 12 healthy participants to evaluate the PK, safety, and tolerability of AMGT-0220 administered at two dose levels (low and high) compared to morphine sulfate and pramipexole. The study will include a screening period, four treatment periods in which a single oral dose of study drug will be administered per treatment period, and an end-of-study (EOS) follow-up visit. Each treatment period will be separated by 3 days. Participants will remain in-house at the study site during the wash-out period to assist with enrollee retention and decrease variability. Each participant will receive all four treatments (A, B, C, and D) in a randomized 4-way crossover design. The four treatments are: A) AMGT-0220 (low dose – 0.125 mg pramipexole/7.5 mg morphine), B) AMGT-0220 (high dose – 0.125 mg pramipexole/15 mg morphine), C) morphine sulfate (15 mg, lowest available strength), D) pramipexole hydrochloride (0.125 mg). During each dosing period, participants will receive one of the 4 assigned treatments. Blood samples will be collected at defined timepoints for analysis of plasma pramipexole, morphine, and morphine metabolites to determine PK parameters. Participants will be monitored for AEs.

**Clinical site and investigator.** This Phase I clinical trial will be carried out PPD's Austin Clinical Research Unit (CRU), which is one of the largest clinics serving both early and late phase study needs. It can accommodate a broad range of NHVs and special populations and is overseen by a Human Safety Committee (HSC) that spans across all CRG Phase I-IV studies to ensure the appropriate safety, medical, and scientific oversight of clinical trial opportunities. This CRU has experience with a broad range of study types, including first-in-human (FIH), single ascending dose/multiple ascending dose, pharmacokinetics/pharmacodynamics, bioavailability/bioequivalence, drug-drug interaction, food effect, thorough QT, human absorption, metabolism and excretion, and age and gender-specific studies. The study Principal Investigator will be led by **Brian Spears, MD**, the Associate Medical Director of Austin CRU, who has been with PPD since 2021. Dr. Spears has 12 years of related experience. Prior to joining PPD, he spent several years in emergency medicine and is a member of the American College of Emergency Physicians.

**Recruitment.** To initiate recruitment, PPD will continuously run multi-channel paid and organic advertising campaigns to instill and maintain interest in trial participation. These efforts will include TV, radio, and social media (e.g., Facebook, Reddit, Instagram) advertising as well as university newsletters, geo-targeting job fairs, and industry sites (e.g. Study Scavenger, Clinical Connections). These ads will drive potential volunteers to register in PPD's database. Continuing optimization based on results and paid study-specific placements, as needed, will drive volunteers to pre-screen for a specific protocol and schedule a consent appointment. At the appointment, potential volunteers will be pre-qualified and educated via an IRB-approved script, and inclusion and exclusion criteria and study timelines will be discussed to assess potential screening failure and drop-out risks.

**Inclusion and exclusion criteria.** The inclusion and exclusion criteria for this study are in **Tables 6 and 7**.

**Table 6: Inclusion criteria for Phase 1 open-label study for AMGT-0220**

|   |
|---|
| 1. Willing and able to provide voluntary written informed consent to participate in the study and written authorization for use and disclosure of protected health information  |
| 2. Male or female between the ages of 18 – 55 years old, inclusive  |
| 3. Healthy with an acceptable medical history (free from significant cardiac, pulmonary, gastrointestinal, hepatic, renal, hematological, neurological, infective, or psychiatric diseases) as determined by medical history over the past 5 years, physical examination, and laboratory tests. |
| 4. Body mass index between <19 and 30 kg/m <sup>2</sup> , inclusive; total body weight of $\geq$ 50 kg (males) or $\geq$ 45.5 (females)   |
| 5. Negative urinalysis for drugs of abuse   |
| 6. Negative serum pregnancy test if of childbearing potential.  |

|  |
|--|
| 7. No vaccines within 7 days of first dose and willing to not receive any vaccine for 7 days after the last dose of study drug.  |
| 8. Has not consumed any prescription drugs, dietary supplements including vitamins and herbal preparations, or non-prescription drugs for 7 days prior to first dose of study drug, except as authorized by the Investigator AND Medical Monitor); agrees to abstain from these substances through the end of study visit (hormonal contraceptives are allowed). |
| 9. Females of childbearing potential must agree to practice a highly effective method of non-hormonal contraception throughout the study period until the EOS visit, unless sterile or postmenopausal.   |
| 10. Males must agree to practice a highly effective method of contraception until the end of study visit or be sterile.  |

**Table 7: Exclusion criteria for Phase 1 open-label study for AMGT-0220**

|   |
|---|
| 1. Has any surgical or medical condition affecting drug absorption (e.g., prior bariatric surgery, gastrectomy, ileal resection)  |
| 2. Currently using prescription drugs, dietary supplements including vitamins and herbal preparations, or non-prescription drugs, susceptible to altering absorption, affecting gastrointestinal motility, changing the gastric pH, increasing or decreasing the metabolism and excretion of the investigational drug |
| 3. History of significant renal, hepatic, cardiovascular, psychiatric, neoplastic, or other diseases which, in the opinion of the Investigator, represent a safety risk for taking part in the study.   |
| 4. Has a history of sensitivity to study drug, or severe drug or other allergies, as judged by the Investigator and any contraindication for either pramipexole or morphine (respiratory depression, asthma or paralytic ileus)   |
| 5. History of drug abuse within previous 2 years or a positive drug screen at Screening and/or Day -1   |
| 6. Regularly consumes alcohol, >21 units per week for males and >14 units per week for females or a positive alcohol urine test at Screening or at CRU admission.   |
| 7. Pregnant or nursing  |
| 8. Positive for hepatitis B surface antigen, hepatitis C virus antibody, or human immunodeficiency virus  |
| 9. Abnormal hematology, blood biochemistry, urinalysis, or ECG considered clinically significant by the Investigator or Sponsor's Medical Monitor.  |
| 10. Receiving or have received another experimental drug within 3 months before study entry   |
| 11. Investigator deems individual as unsuitable for participation in this trial for any reason  |
| 12. Donated blood or had significant blood loss (greater than 500 mL) within 8 weeks of Screening.  |
| 13. Participated in a clinical trial within 3 months of Screening, or within a period of less than 5 half-lives, or double duration of the biological effect of the investigational product received (whichever is longer).   |
| 14. Unwilling or unable to follow the procedures specified by the protocol  |

**Screening.** Screening of potential participants will include body weight and body mass index, urinalysis for drugs of abuse (i.e., amphetamines, barbiturates, cannabinoids, cocaine metabolites, or opiates), serum pregnancy test and screening for hepatitis B surface antigen, hepatitis C virus antibody, and human immunodeficiency virus, complete blood counts, blood biochemistry, and electrocardiogram (ECG)

**Randomization.** After screening, each participant will receive all four treatments (A, B, C, and D - see **Fig. 7**) in a randomized 4-way crossover design, with a 3-day washout period between each treatment period.

**Primary and secondary objectives.** The primary objective of this study is to compare the plasma pharmacokinetics (PK) of morphine (and metabolites: morphine-3-glucuronide and morphine-6-glucuronide) and pramipexole when administered in combination (AMGT-0220) relative to alone at low and high dose. The secondary objective is to investigate the safety and tolerability of AMGT-0220 in healthy participants.

**Risks and mitigation of risks.** Potential risks to consider are AEs due to the combination and failure to recruit the target number of participants or loss of participants due to dropping out of the study. To mitigate the risk of AEs, patients will be closely monitored, and the study paused if any significant AEs are identified in order to understand the cause. To mitigate the risk of recruitment or drop out failures, we have selected a CRO, PPD, with a demonstrated ability to recruit healthy patients for Phase 1 studies. Moreover, volunteers will be housed within the PPD facility to further reduce the risk of dropouts.

**Study interventions.** Each participant will receive each the following oral treatments in a randomized order: A) AMGT-0220 (low dose) containing 0.125 mg pramipexole/7.5 mg morphine; B) AMGT-0220 (high dose) containing 0.125 mg pramipexole/15 mg morphine; C) morphine sulfate (Hikma, NDA 022195; 15 mg, the lowest available strength); D) pramipexole hydrochloride (ANDA 090781; 0.125 mg). During each dosing period, participants will receive one of the 4 assigned treatments. Participants will fast overnight for a minimum of 10 h prior to drug

administration and for up to 4 h post-dosing. Water will be allowed except for 1 h before and 1 h after administration, except for that required for drug delivery (up to 240 mL).

**PK assessments.** On each dosing day of each treatment period, 16 blood samples (5 mL/sample) will be collected from each participant at the following time points: predose; 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, and 24 h post-dose. Morphine, morphine-3-glucuronide, morphine-6-glucuronide and/or pramipexole in the plasma for each subject will be measured by LC-MS/MS using validated methods. The PK parameters to be calculated will include the maximum plasma concentration (Cmax), time to reach maximum plasma concentration (Tmax), cumulative area under the plasma concentration-time curve (AUC<sub>T</sub>), area under the curve extrapolated to infinity (AUC<sub>∞</sub>), relative percentage of AUC<sub>T</sub> to AUC<sub>∞</sub> (AUC<sub>T/∞</sub>), apparent elimination rate constant (Kel), half-life of elimination (T<sub>1/2el</sub>), apparent volume of distribution (VD/F), and apparent plasma clearance (Cl/F).

**Safety assessments.** Monitoring for AEs will include 12-lead ECGs, vital sign measurements, pulse oximetry, clinical laboratory tests, and physical examination. At completion of the study, AEs will be tabulated.

**Statistical methods.** To avoid statistical inference, Cmax, AUC<sub>T</sub>, and AUC<sub>∞</sub> will be normalized by dose and transformed using the natural logarithm (ln), while Tmax will be rank transformed. A non-compartmental approach, assuming a log-linear terminal phase, will be employed to estimate PK parameters. The AUC will be determined by the trapezoidal rule, with the terminal phase estimated by maximizing the coefficient of determination from the log-linear regression model. To compare Cmax and AUC parameters between the test and reference drugs, a paired t-test will be employed, as the study follows a crossover design where each participant serves as their own control. The logarithmic transformation of Cmax and AUC values will be performed prior to analysis to stabilize variance and approximate normal distribution. The differences in the log-transformed values between the test and reference drugs will then be analyzed using the paired t-test. The results will be back-transformed to obtain the geometric mean ratios, and the corresponding 90% confidence intervals will be calculated. If these intervals lie entirely within the bioequivalence range of 80% to 125%, bioequivalence will be established. This approach aligns with regulatory guidelines and provides a rigorous test of whether the test drug can be considered bioequivalent to the reference.

**Expected outcomes, pitfalls, and alternative approaches.** The goal of this study is to obtain pK data for this combination ahead of a Phase 2 study. Based on the long clinical histories of pramipexole and morphine and discussions with the FDA, we expect this to be achieved. If we observe that one drug affects the metabolism of the other, we will reformulate the combination to address this issue. As the doses of pramipexole and morphine in AMGT-0220 are below the prescribed therapeutic dose levels for these agents, we do not anticipate observing any significant AEs.

## SUMMARY AND TIMELINE

| Table 8: Summary and Project Timeline   |        |     |     |     |      |       |       |
|---|--------|-----|-----|-----|------|-------|-------|
| Phase I   | Months |     |     |     |      |       |       |
|   | 1      | 2   | 3   | 4   | 5    | 6     |       |
| <b>Aim 1 Manufacture clinical batches of AMGT-0220 drug product</b>                     |        |     |     |     |      |       |       |
| 1.1 Complete manufacturing of clinical batches  |        |     |     |     |      |       |       |
| 1.2 Release of AMGT-0220 clinical batch   |        |     |     |     |      |       |       |
| <b>Aim 2 Submit an IND application for AMGT-0220</b>                                    |        |     |     |     |      |       |       |
| 2.1 Prepare eCTD compliant reports for Modules 4&5                                      |        |     |     |     |      |       |       |
| 2.2 Complete preparation of Modules 1–3   |        |     |     |     |      |       |       |
| 2.3 Submit IND application to the FDA   |        |     |     |     |      |       |       |
| <b>Go/No-Go:</b> FDA receives IND package   |        |     |     |     |      |       |       |
| Phase II  |        |     |     |     |      |       |       |
| Milestone   | 1/2    | 3/4 | 5/6 | 7/8 | 9/10 | 11/12 | 13/14 |
|   | 1/2    | 3/4 | 5/6 | 7/8 | 9/10 | 11/12 | 13/14 |
| <b>Aim 1 Conduct a Phase 1 single-dose PK clinical trial in healthy volunteers</b>      |        |     |     |     |      |       |       |
| 1.1 Bioanalytical development and validation  |        |     |     |     |      |       |       |
| 1.2 Determine the PK profile and safety/tolerability of AMGT-0220 in healthy volunteers |        |     |     |     |      |       |       |

A summary of the Approach and the timeline for related tasks are presented in **Table 8**. Successful completion of this SBIR Fast-Track project will provide critical in-human PK data to support the design of future clinical trials. Opioids continue to be the standard of care for moderate to severe pain. With no effective non-opioid drugs on the horizon, a novel medication delivering effective opioid analgesia while mitigating the inherent risks of OUD and tolerance is set to take a significant portion of the market to provide pain patients with a needed alternative to high-dose opioid monotherapy.

## PHS Human Subjects and Clinical Trials Information

OMB Number: 0925-0001

Expiration Date: 01/31/2026

### Use of Human Specimens and/or Data

Does any of the proposed research in the application involve human specimens and/or data \*

Yes  No

Provide an explanation for any use of human specimens and/or data not considered to be human subjects research.

Are Human Subjects Involved

Yes  No

Is the Project Exempt from Federal regulations?

Yes  No

Exemption Number

1  2  3  4  5  6  7  8

Other Requested Information

**Human Subject Studies**

| <b>Study#</b> | <b>Study Title</b>   | <b>Clinical Trial?</b> |
|---------------|--|------------------------|
| 1             | A PHASE 1, OPEN-LABEL STUDY IN HEALTHY VOLUNTEERS TO EVALUATE THE SAFETY, PHARMACOKINETICS AND RELATIVE BIOAVAILABILITY OF AMGT-0220 AT LOW AND HIGH DOSE LEVELS COMPARED TO MORPHINE AND PRAMIPEXOLE ADMINISTRATION ALONE | Yes                    |

## Section 1 - Basic Information (Study 1)

### 1.1. Study Title \*

A PHASE 1, OPEN-LABEL STUDY IN HEALTHY VOLUNTEERS TO EVALUATE THE SAFETY, PHARMACOKINETICS AND RELATIVE BIOAVAILABILITY OF AMGT-0220 AT LOW AND HIGH DOSE LEVELS COMPARED TO MORPHINE AND PRAMIPEXOLE ADMINISTRATION ALONE

### 1.2. Is this study exempt from Federal Regulations \*

Yes       No

### 1.3. Exemption Number

1     2     3     4     5     6     7     8

### 1.4. Clinical Trial Questionnaire \*

1.4.a. Does the study involve human participants?       Yes       No

1.4.b. Are the participants prospectively assigned to an intervention?       Yes       No

1.4.c. Is the study designed to evaluate the effect of the intervention on the participants?       Yes       No

1.4.d. Is the effect that will be evaluated a health-related biomedical or behavioral outcome?       Yes       No

### 1.5. Provide the ClinicalTrials.gov Identifier (e.g. NCT87654321) for this trial, if applicable

## Section 2 - Study Population Characteristics (Study 1)

### 2.1. Conditions or Focus of Study

- The focus of this study is to determine the plasma pharmacokinetics of morphine (and metabolites) and pramipexole when administered in combination (AMGT-0220) relative to those of the individual reference drugs administered alone
- A second focus of the study is to investigate the safety and tolerability of AMGT-0220 in healthy participants

### 2.2. Eligibility Criteria

#### Inclusion Criteria:

1. Are willing and able to provide voluntary written informed consent for the participant to participate in the study and written authorization for use and disclosure of protected health information
2. Are a male or female between the ages of 18 – 55 years old, inclusive
3. Be healthy and have an acceptable medical history (defined as individuals who are free from significant cardiac, pulmonary, gastrointestinal, hepatic, renal, hematological, neurological, infective, or psychiatric diseases as determined by medical history over the past 5 years, physical examination, and laboratory tests)
4. Have a body mass index between <19 and 30 kg/m<sup>2</sup>, inclusive and have a total body weight of  $\geq 50$  kg (males) or  $\geq 45.5$  (females)
5. Have a negative urinalysis for drugs of abuse, such as amphetamines, barbiturates, cannabinoids, cocaine metabolites, or opiates
6. Have a negative serum pregnancy test at screening if female and of childbearing potential.
7. Have not had any vaccine within 7 days of the first dose of study drug and, willing to not receive any vaccine for 7 days after receiving the last dose of study drug.
8. Has not consumed any prescription drugs, dietary supplements including vitamins and herbal preparations, or non-prescription drugs (except as authorized by the Investigator AND Medical Monitor) for 7 days prior to first dose of study drug and agrees to abstain from these substances through the end of study (EOS) visit. Note, hormonal contraceptives are allowed.
9. If female and of childbearing potential, must agree to practice a highly effective method of non-hormonal contraception throughout the study period until the EOS visit, unless sterile or postmenopausal.
10. Males participating in the study, must agree to practice a highly effective method of contraception throughout the study period until the end of study visit, or be sterile.

#### Exclusion Criteria:

1. Has any surgical or medical condition affecting drug absorption (e.g., prior bariatric surgery, gastrectomy, ileal resection)
2. Is currently using prescription drugs, dietary supplements including vitamins and herbal preparations, or non-prescription drugs, susceptible to altering absorption, affecting gastrointestinal motility, changing the gastric pH, increasing or decreasing the metabolism and excretion of the investigational drug
3. Has a history of significant renal, hepatic, cardiovascular, psychiatric, neoplastic, or other diseases which, in the opinion of the Investigator, represent a safety risk for taking part in the study.
4. Has a history of sensitivity to study drug, or severe drug or other allergies, as judged by the Investigator and any contraindication for either pramipexole or morphine (respiratory depression, asthma or paralytic ileus).
5. Has a history of drug abuse within the previous 2 years, or a positive drug screen (at minimum, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, and opiates) at Screening and/or Day -1.
6. Regularly consumes alcohol, >21 units per week for males and >14 units per week for females (one unit is equivalent to 220 to 250 mL of beer or 125 mL of wine or 25 mL of 40% spirits), or a positive alcohol urine test at Screening or at CRU admission.
7. Is pregnant or nursing
8. Has positive hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (anti HCV), or human immunodeficiency virus (HIV) test results at Screening.
9. Has abnormal hematology, blood biochemistry, urinalysis, or ECG findings that are considered clinically significant by the Investigator or Sponsor's Medical Monitor.
10. Is receiving or have received another experimental drug within 3 months before study entry
11. Is assessed by the investigator as unsuitable for participation in this trial for any reason
12. Has donated blood had significant blood loss (greater than 500 mL) within 8 weeks prior to Screening.
13. Participated in a clinical trial within 3 months prior to Screening, or within a period of less than 5 half-lives, or double duration of the biological effect of the investigational product received (whichever is longer).
14. Is unwilling or unable to follow the procedures specified by the protocol.

### 2.3. Age Limits

Min Age: 18 Years

Max Age: 55 Years

### 2.3.a. Inclusion of Individuals Across the Lifespan

Inclusion\_lifespan\_AT\_FT\_2024.08.31.pdf

### 2.4. Inclusion of Women and Minorities

Inclusion\_women\_minorities\_AT\_FT\_2024.08.31.pdf

### 2.5. Recruitment and Retention Plan

Recruit\_plan\_AT\_FT\_2024.08.31.pdf

|                                      |                    |             |
|--------------------------------------|--------------------|-------------|
| 2.6. Recruitment Status              | Not yet recruiting |             |
| 2.7. Study Timeline                  | Timeline.pdf       |             |
| 2.8. Enrollment of First Participant | 12/02/2025         | Anticipated |

## **INCLUSION OF INDIVIDUALS ACROSS LIFESPAN**

The proposed Phase 1 clinical study is focused on determining the pharmacokinetics, tolerability, and safety of a novel fixed-dose pain medication in healthy volunteers. As such, the proposed trial will focus on patients that are between 18 and 55 years of age. This age range are likely not to be associated with significant underlying medical conditions, allowing Amalgent Therapeutics to assess their drug's safety and potential side effects before it is given to those with the intended medical condition (moderate or severe pain) or other underlying medical condition. As the medication is initially intended to be used for adults with acute pain, the trial will focus on patients that are at least 18 years old.

### **INCLUSION OF WOMEN AND MINORITIES**

The proposed Phase 1 clinical study is focused on determining the pharmacokinetics, tolerability, and safety of a novel pain medication in healthy volunteers. Subjects will be enrolled equally between men and women. Race/ethnicity of subjects will not have any bearing on the proposed clinical study. Therefore, we will accept subjects from any race, gender, or ethnic background if they consent to participate in the study.

## **RECRUITMENT AND RETENTION PLAN**

To initiate recruitment, PPD, the clinical research organization that will run the study within their Austin, Texas facility, will continuously run multi-channel paid and organic advertising campaigns to instill and maintain interest in trial participation. These efforts will include TV, radio, and social media (e.g., Facebook, Reddit, Instagram) advertising as well as university newsletters, geo-targeting job fairs, and industry sites (e.g. Study Scavenger, Clinical Connections). These ads will drive potential volunteers to register in PPD's database. Continuing optimization based on results and paid study-specific placements, as needed, will drive volunteers to pre-screen for a specific protocol and schedule a consent appointment. At the appointment, potential volunteers will be pre-qualified and educate potential volunteers via an IRB-approved script, and inclusion and exclusion criteria and study timelines will be discussed to assess potential screening failure and drop-out risks.

The Clinical Research Unit in Austin, Texas has 200 beds for both early and late phase clinical pharmacology studies, specifically designed to accommodate either short-term or long-term stays. To assist retention, participants will remain in the facility for the duration of the study.

| Activity   | Pre | Y1      |         |         |         | Y2      |          |
|--|-----|---------|---------|---------|---------|---------|----------|
|  | Q3  | Q4 2025 | Q1 2026 | Q2 2026 | Q3 2026 | Q4 2026 | Q1+ 2027 |
| Completion of protocol, site contracts, clinicaltrials.gov registration, IRB approval, IND update    | ■   |         |         |         |         |         |          |
| Bioanalytical method development and validation, including stability in human plasma                 |     | ■       |         |         |         |         |          |
| Recruitment and enrollment   |     |         | ■       |         |         |         |          |
| Treatment period Complete sample collection and ship for analysis                                    |     |         |         | ■       |         |         |          |
| Bioanalytical analysis with report   |     |         |         |         | ■       |         |          |
| Biostatistical analysis, complete final report, report results to ClinicalTrials.gov,                |     |         |         |         | ■       | ■       |          |
| Submission of publication of results, present at scientific meetings, meet with key opinions leaders |     |         |         |         |         | ■       | ■        |

2.9. Inclusion Enrollment Reports

| IER ID#               | Enrollment Location Type | Enrollment Location |
|-----------------------|--------------------------|---------------------|
| <u>Study 1, IER 1</u> | Domestic                 | Austin, Texas       |

## Inclusion Enrollment Report 1

1. Inclusion Enrollment Report Title\* :

Inclusion enrollment for Phase 1, randomized, open-label, four-period, single-dose, crossover study in 12 healthy participants to evaluate the PK, safety, and tolerability of AMGT-0220 administered at 2 dose levels (low and high) compared to morphine sulfate and pramipexole

2. Using an Existing Dataset or Resource\* :

Yes       No

3. Enrollment Location Type\* :

Domestic       Foreign

4. Enrollment Country(ies):

USA: UNITED STATES

5. Enrollment Location(s):

Austin, Texas

6. Comments:

Subjects will be enrolled equally between men and women. Race/ethnicity of subjects will not have any bearing on the proposed clinical study. Therefore, we will accept subjects from any race, gender, or ethnic background if they consent to participate in the study.

### Planned

| Racial Categories                            | Ethnic Categories      |          |                    |          | Total     |  |
|--|------------------------|----------|--------------------|----------|-----------|--|
|  | Not Hispanic or Latino |          | Hispanic or Latino |          |           |  |
|  | Female                 | Male     | Female             | Male     |           |  |
| American Indian/<br>Alaska Native            | 0                      | 0        | 0                  | 0        | 0         |  |
| Asian  | 0                      | 0        | 0                  | 0        | 0         |  |
| Native Hawaiian or<br>Other Pacific Islander | 0                      | 0        | 0                  | 0        | 0         |  |
| Black or African<br>American                 | 2                      | 2        | 0                  | 0        | 4         |  |
| White  | 2                      | 2        | 2                  | 2        | 8         |  |
| More than One Race                           | 0                      | 0        | 0                  | 0        | 0         |  |
| <b>Total</b>                                 | <b>4</b>               | <b>4</b> | <b>2</b>           | <b>2</b> | <b>12</b> |  |

### Cumulative (Actual)

| Racial Categories                            | Ethnic Categories      |          |                          |                    |          |                          |                                |          |                          | Total    |  |
|--|------------------------|----------|--------------------------|--------------------|----------|--------------------------|--------------------------------|----------|--------------------------|----------|--|
|  | Not Hispanic or Latino |          |                          | Hispanic or Latino |          |                          | Unknown/Not Reported Ethnicity |          |                          |          |  |
|  | Female                 | Male     | Unknown/<br>Not Reported | Female             | Male     | Unknown/<br>Not Reported | Female                         | Male     | Unknown/<br>Not Reported |          |  |
| American Indian/<br>Alaska Native            | 0                      | 0        | 0                        | 0                  | 0        | 0                        | 0                              | 0        | 0                        | 0        |  |
| Asian  | 0                      | 0        | 0                        | 0                  | 0        | 0                        | 0                              | 0        | 0                        | 0        |  |
| Native Hawaiian or<br>Other Pacific Islander | 0                      | 0        | 0                        | 0                  | 0        | 0                        | 0                              | 0        | 0                        | 0        |  |
| Black or African<br>American                 | 0                      | 0        | 0                        | 0                  | 0        | 0                        | 0                              | 0        | 0                        | 0        |  |
| White  | 0                      | 0        | 0                        | 0                  | 0        | 0                        | 0                              | 0        | 0                        | 0        |  |
| More than One Race                           | 0                      | 0        | 0                        | 0                  | 0        | 0                        | 0                              | 0        | 0                        | 0        |  |
| Unknown or<br>Not Reported                   | 0                      | 0        | 0                        | 0                  | 0        | 0                        | 0                              | 0        | 0                        | 0        |  |
| <b>Total</b>                                 | <b>0</b>               | <b>0</b> | <b>0</b>                 | <b>0</b>           | <b>0</b> | <b>0</b>                 | <b>0</b>                       | <b>0</b> | <b>0</b>                 | <b>0</b> |  |

### Section 3 - Protection and Monitoring Plans (Study 1)

3.1. Protection of Human Subjects [Protection\\_HS\\_AT\\_FT\\_2024.08.31.pdf](#)

3.2. Is this a multi-site study that will use the same protocol to conduct non-exempt human subjects research at more than one domestic site?

Single IRB plan attachment

3.3. Data and Safety Monitoring Plan [Data-Safety\\_Monitoring\\_AT\\_FT\\_2024.08.30.pdf](#)

3.4. Will a Data and Safety Monitoring Board be appointed for this study?

Yes  No  N/A

3.5. Overall structure of the study team

## PROTECTION OF HUMAN SUBJECTS

### 1. Risks to Human Subjects

#### A. Human Subjects Involvement, Characteristics, and Design

**Study Design:** This is a Phase 1, randomized, open-label, four-period, single-dose, crossover study in 12 healthy participants to evaluate the PK, safety, and tolerability of AMGT-0220 administered at 2 dose levels (low and high) compared to morphine sulfate and pramipexole.

The study consists of a screening period, 4 treatment periods with a single oral dose of study drug per treatment period, and an end-of-study (EOS) follow-up visit. Each treatment period will be separated by 3 days. The investigator has the flexibility to keep participants in-house or discharge during the washout of 3 days.

Each participant will receive all four treatments (A, B, C, and D) in a randomized 4-way crossover design. The four treatments are:

AMGT-0220 (low dose) = 0.125 mg pramipexole/7.5 mg morphine  
AMGT-0220 (high dose) = 0.125 mg pramipexole/15 mg morphine  
Morphine sulfate (Hikma, NDA 022195) = 15 mg (lowest available strength)  
Pramipexole Hydrochloride (ANDA 090781) = 0.125 mg

**Subject population(s) to be included in the study:** 6 adult women and 6 adult men between the ages of 18 and 55 years. Race/ethnicity of subjects will not have any bearing on the proposed clinical study. Therefore, we will accept subjects from any race, gender, or ethnic background if they consent to participate in the study. We will aim as much as possible to have an even distribution across the demographics.

**Collaborating Site:** PPD Austin Clinical Research Unit: A dedicated Screening Enrollment Coordinator will organize screening and obtain informed consent for those who pass the inclusion criteria. The Principal Investigator for the study will be Dr. Brian Spears, Associate Medical Director of the site.

#### B. Study Procedures, Materials, and Potential Risks

Each participant will receive each the following oral treatments in a randomized order:

- i. AMGT-0220 (low dose) = 0.125 mg pramipexole / 7.5 mg morphine
- ii. AMGT-0220 (high dose) = 0.125 mg pramipexole / 15 mg morphine
- iii. Morphine sulfate (Hikma, NDA 022195) = 15 mg (lowest available strength)
- iv. Pramipexole Hydrochloride (ANDA 090781) = 0.125 mg

During each dosing period, participants will receive one of the 4 assigned treatments. Participants will fast overnight for a minimum of 10 hours prior to drug administration and for up to 4 hours after dosing. Water will be allowed except for 1 hour before and 1 hour after administration, except for that required for drug delivery (up to 240 mL).

### 2. Adequacy of Protection Against Risks

#### A. Informed Consent and Assent

Protocol specific pre-qualification and education via an IRB approved script along with inclusion and exclusion criteria and study timelines will be discussed with potential volunteers. Those passing the inclusion criteria and willing to participate sign provide signed informed consent. All interviews with the subjects, including the informed consent interview, will be conducted privately.

Patients who lack the capacity to consent, who require a legally authorized representative, or who are unable to consent will not participate in the study.

#### B. Protections Against Risk

Private identifiable information from medical records could be a risk if exposed. However, all members of the study team are trained in data security, and procedures are in place to regularly audit data security compliance.

There is a risk to potential adverse events from the combination. This risk is low based on a previous study in which morphine and pramipexole were combined but administered as single agents. To mitigate the risk, participants will remain in the Clinical Research Unit for the duration of the study. They will be closely

monitored, and the study paused if any significant AEs are identified in order to understand the cause. Healthy volunteers are also being used in this study to prevent unforeseen adverse events due to underlying health conditions.

**C. Populations that are vulnerable to coercion or undue influence and pregnant women, fetuses and neonates, if relevant to your study**

The proposed study does not include any populations that NIH considers vulnerable.

**3. Potential Benefits of the Proposed Research to Research Participants and Others**

- a. There are no direct, potential benefits to research participants.
- b. The proposed research will generate critical data on the pharmacokinetics, tolerability, and safety of Amalgent's AMGT-0220, a novel pain medication that combines low-dose (subtherapeutic dose) of morphine with an adjuvant pramipexole. This combination is expected to be as effective as full-strength morphine (a commonly used opioid pain medication) but without the risk of tolerance or addiction. For patients for whom non-opioid pain medications are ineffective, opioid pain medications are the only source of relief but come with the risk of developing tolerance where the drugs no longer work or becoming addicted. Successful completion of this clinical trial will provide valuable information to allow Amalgent to proceed with important clinical trials in the indicated condition. As the population ages, more people are affected by moderate to severe pain. Thus, the development of a safer, more effective opioid will be beneficial for all those suffering from acute and chronic moderate to severe pain.

**4. Importance of the Knowledge to be Gained**

- a. Opioids are highly effective analgesics and a critical therapeutic resource for treating moderate to severe pain. They are used to treat pain related to oncology, surgery, and acute injuries (e.g., fractures, sprains, and burns) as well as chronic pain (e.g., osteoarthritis, back pain, and neuropathic pain) unmanaged by non-opioid medications. More than half of the 18 million patients undergoing surgery each year receive postoperative opioids. Although powerful pain medications, about 3–19% of patients prescribed an opioid will develop opioid use disorder (OUD), including dependence and addiction or will develop tolerance such that the drug no longer works. Despite the opioid crisis, no non-opioid drugs have been approved that can completely replace opioids for moderate and severe pain. Amalgent is developing a low-dose opioid drug that mitigates the risks of current opioid therapies while maintaining their superior analgesia. This Phase 1 trial is the first step in bringing the important medication to pain sufferers. This study will enable us to understand whether the two drug components within AMGT-0220 achieve appropriate drug levels and that each drug does not interfere with the bioavailability of the other. It will also demonstrate the safety and tolerability of this novel agent. This information is vital to designing future studies with pain patients. The risk for complications and side effects of full strength opioids is high (respiratory depression, toxicity to the central nervous system, increased intracranial pressure, nausea, constipation, and hypotension). The doses of either drug are lower than the lowest doses of the two agents prescribed individually and thus the risk to the volunteers is low. Thus, the risks are reasonable in relation to the importance of the knowledge that we expect to gain from the results.

## **DATA AND SAFETY MONITORING PLAN**

The clinical trial protocol will be submitted as part of the IND package that will be prepared and submitted in Phase I of this Fast Track project. PPD on behalf of Amalgent Therapeutics, Inc will evaluate the progress of the study, to review procedures for maintaining confidentiality of data, the quality of data collection, management and analysis. The contracted CRO will assign a Clinical Study Monitor and a Medical Monitor (TBD) that will be responsible for daily monitoring. This trial will be conducted in compliance with all applicable federal regulations pertaining to investigational drugs, including but not limited to: 21 CFR Part 50, Part 54, Part 56, Part 312, and GCP standards. The protocol will be approved by the Institutional Review Board (IRB) of the Austin Clinical Research Unit where the study will be performed, and the study will be conducted in compliance with the approved protocol. Any deviations from the protocol that could affect the safety and welfare of study participants will be immediately reported to the Sponsor and the IRB.

### **Frequency of Data Monitoring**

All data relating to study procedures will be entered into Case Report Forms (CRFs) provided by PPD on behalf of Amalgent. All requested information must be entered on the CRF, and there should be a CRF completed for each study participant. If an item is not available or applicable, this fact should be indicated. Any assessment that is performed on a subject while they are participating in the study, must be recorded in the CRF. Once available and prior to any subject being enrolled, a blank version of the planned CRF data fields and database training will be provided by PPD. The completed CRFs are the sole property of the Sponsor and should not be made available in any form to third parties without written permission from the Sponsor.

Data will be entered into a computer database that is specific for this trial. Access to the database will be restricted to personnel responsible for data entry and to data management and statistics personnel, who are directly involved in the management or analysis of this trial. Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Investigator, Dr. Spears. The study eCRF is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, and timeliness of the data reported in the eCRFs and all other required reports. Data reported on the eCRFs, which are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the eCRF must be recorded. Any missing data must be explained. For electronic CRFs an audit trail will be maintained by the system. Obvious errors (self-evident corrections) will be corrected and documented by the Sponsor or its designee. Other errors or omissions will result in queries which will be sent to the investigational site on Data Clarification Forms (DCF)/Query Forms for resolution. A copy of the signed DCF is to be kept by the site with the CRFs. Once the original is received by the Sponsor or its designee, the resolutions will be reviewed and entered into the database. During the course of the trial, data queries will be generated for data items that are potentially erroneous and require appropriate clarification or correction. Prior to database lock, statistical verification of the data will be undertaken in order to further assure data quality.

All information provided regarding the study, as well as all information collected/documentated during the course of the study will be regarded as confidential. The Investigator agrees not to disclose such information in any way without prior written permission from the Sponsor. Any publication of the results, either in part or in total (articles in journals, oral presentations, abstracts, etc.) by the Investigator or their representative(s), shall require prior notification and review, within a reasonable time frame, by the Sponsor.

The investigator/institution should maintain trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents. Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

### **Frequency of Safety Monitoring and Reporting**

Serious Adverse Events/Experiences (SAEs) will be recorded following the first study drug administration through the end-of-treatment follow-up (3-5 days after the last dose). Any serious adverse event that occurs during this investigation, whether or not related to the study medication, must be reported immediately (within 48 hours) to the study sponsor and clinical lead. All AEs occurring during the study are to be followed up in accordance with good clinical practice until they are resolved, stabilized or judged no longer clinically significant or, if a chronic condition, until fully characterized. Any AEs that are considered drug-related (possibly related, related) must be followed until resolution or until stabilization. The Investigator will be required to provide complete information concerning each SAE to the Sponsor within 5 calendar days of the event. This information

must be recorded in the patient's medical record and then transcribed onto the SAE Form. The completed SAE Form (including the Investigator's opinion of the relationship of the SAE to the study medication), copies of related results/reports, consultant report(s), and other relevant information will be faxed and mailed to the Sponsor. In the event of an SAE leading to hospitalization, every effort will be made by the investigational site to obtain medical records, including a hospital discharge summary. In the event of a fatal AE, documentation of any available postmortem findings, including autopsy, will be provided to Amalgent or their designee. In any event, the Investigator will provide a narrative summary of circumstances, events related to the death, and cause of death, if known. Any follow-up information obtained must be recorded on an SAE follow-up report form. The Investigator must comply with the applicable local regulatory requirements related to the reporting of SAEs to regulatory authorities and the Institutional Review Board (IRB). Upon receipt from Amalgent of an initial or follow-up IND Safety Report or other safety information, the Investigator must promptly notify his or her IRB. All AEs and SAEs will be reported on an annual basis to FDA in accordance with the IND regulation (21 CFR Part 312). Per the 2010 FDA Guidance Document for Industry and Investigators "Safety Reporting Requirements for INDs and BA/BE Studies," events categorized as 'possibly' or 'probably' related will be treated as 'suspected adverse reactions.' Events categorized as 'definitely' related will be treated as an 'adverse reaction.' All serious, unexpected adverse reactions and suspected adverse reactions will be reported to FDA and to all participating Investigators as an IND Safety Report within 15 calendar days of the event after the sponsor determines that the suspected adverse reaction qualifies for reporting (21 CFR §312.32). Any unexpected fatal or life-threatening AEs will be reported to the Agency within 7 calendar days after the sponsor's initial receipt of the information. The Sponsor will notify all participating Investigators of any new safety information that alters the current risk-benefit assessment of the study medication or that would be sufficient to consider changes in administration or in the overall conduct of the trial.

### **Protection of Confidentiality**

In accordance with Good Clinical Practice and with the national data protection laws, all information concerning the subjects in the study must be treated as strictly confidential by all persons involved in the study. The Investigator acknowledges that any and all information acquired from the Sponsor or its designee or developed or acquired in connection with the study are strictly confidential. The Investigator will not disclose any confidential information to any third party nor use confidential information for any purpose without first obtaining the consent of Sponsor in writing. Such consent shall be deemed to have been given for disclosure to any person for whom the Investigator is responsible at his/her center, but only so far as required for the purposes of the study, and, in the case of disclosures to staff, only if such staff are bound by obligations of confidentiality no less strict than those set out herein.

## Section 4 - Protocol Synopsis (Study 1)

### 4.1. Study Design

#### 4.1.a. Detailed Description

This is a Phase 1, randomized, open-label, four-period, single-dose, crossover study in 12 healthy participants to evaluate the PK, safety, and tolerability of AMGT-0220 administered at 2 dose levels (low and high) compared to morphine sulfate and pramipexole.

The study consists of a screening period, 4 treatment periods with a single oral dose of study drug per treatment period, and an end-of-study (EOS) follow-up visit. Each treatment period will be separated by 3 days. The investigator has the flexibility to keep participants in-house or discharge during the washout of 3 days.

Each participant will receive all four treatments (A, B, C, and D) in a randomized 4-way crossover design. The four treatments are:

- A. AMGT-0220 (low dose) = 0.125 mg pramipexole/7.5 mg morphine
- B. AMGT-0220 (high dose) = 0.125 mg pramipexole/15 mg morphine
- C. Morphine sulfate (Hikma, NDA 022195) = 15 mg (lowest available strength)
- D. Pramipexole Hydrochloride (ANDA 090781) = 0.125 mg

#### Study Population:

Healthy participants will be recruited for this study. An equal number of males and females will be enrolled. Participants must meet all of the following criteria

#### Study Intervention:

Each participant will receive each the following oral treatments in a randomized order. During each dosing period, participants will receive one of the 4 assigned treatments. Participants will fast overnight for a minimum of 10 hours prior to drug administration and for up to 4 hours after dosing. Water will be allowed except for 1 hour before and 1 hour after administration, except for that required for drug delivery (up to 240 mL).

#### Safety Assessments:

Safety will be monitored through AEs, 12-lead ECGs, vital sign measurements, pulse oximetry, clinical laboratory tests, and physical examination. AEs will be tabulated and summary statistics provided for the 12-lead ECGs, vital signs, and clinical laboratory tests may be computed and provided, as deemed clinically appropriate.

#### PK Assessments:

On each dosing day for each treatment period a total of 16 blood samples (5 mL) will be collected from each participant for PK analyses of morphine (and metabolites: morphine-3-glucuronide and morphine-6-glucuronide) and pramipexole at the following time points: predose and 15, 30, 45 minutes and at 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16 and 24 hours post dose.

The following PK parameters will be calculated, as data allows, using noncompartmental analysis, for morphine, morphine-3-glucuronide, morphine-6-glucuronide and pramipexole in plasma for each treatment:

- AUClast
- AUCinf
- Cmax
- Tmax
- t<sub>1/2</sub>

#### 4.1.b. Primary Purpose

#### Other

To compare the plasma pharmacokinetics (PK) of morphine (and metabolites: morphine 3-glucuronide and morphine-6-glucuronide) and pramipexole when administered in combination (AMGT-0220) relative to alone (RLDs) at low and high dose

#### 4.1.c. Interventions

| Type                     | Name                  | Description   |
|--------------------------|-----------------------|---|
| Drug (including placebo) | AMGT-0220 (low dose)  | An tablet containing 0.125 mg pramipexole and 7.5 mg morphine |
| Drug (including placebo) | AMGT-0220 (high dose) | n tablet containing 0.125 mg pramipexole and 15 mg morphine   |

|                          |                           |                               |
|--------------------------|---------------------------|-------------------------------|
| Drug (including placebo) | Morphine sulfate          | Hikma, NDA 02219 15 mg tablet |
| Drug (including placebo) | Pramipexole Hydrochloride | ANDA 090781 0.125 mg          |

4.1.d. Study Phase Phase 1

Is this an NIH-defined Phase III Clinical Trial?  Yes  No

4.1.e. Intervention Model Cross-Over

4.1.f. Masking  Yes  No

□ Participant □ Care Provider □ Investigator □ Outcomes Assessor

4.1.g. Allocation Randomized

## 4.2. Outcome Measures

| Type      | Name                   | Time Frame                   | Brief Description  |
|-----------|------------------------|------------------------------|--|
| Primary   | PK parameters          | 24 hours for each dosing day | On each dosing day for each treatment period a total of 16 blood samples (5 mL) will be collected from each participant for PK analyses of morphine (and metabolites: morphine-3-glucuronide and morphine-6-glucuronide) and pramipexole at the following time points: predose and 15, 30, 45 minutes and at 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16 and 24 hours post dose. PK parameters: AUClast, AUCinf, Cmax, Tmax, t½ |
| Secondary | • Adverse events (AEs) | 24 hours for each dosing day | Safety will be monitored through AEs, 12-lead ECGs, vital sign measurements, pulse oximetry, clinical laboratory tests, and physical examination. AEs will be tabulated and summary statistics provided for the 12-lead ECGs, vital signs, and clinical laboratory tests may be computed and provided, as deemed clinically appropriate  |

4.3. Statistical Design and Power Trial\_Info\_AMGT-0220\_SAP\_090324.pdf

4.4. Subject Participation Duration 9 weeks

4.5. Will the study use an FDA-regulated intervention?  Yes  No

4.5.a. If yes, describe the availability of Investigational Product (IP) and Investigational New Drug (IND)/ Investigational Device Exemption (IDE) status IND\_STATUS\_2024.08.31\_(1).pdf

4.6. Is this an applicable clinical trial under FDAAA?  Yes  No

4.7. Dissemination Plan DISSEMINATION\_AT\_RT\_2024.08.31.pdf

## STATISTICAL ANALYSIS PLAN FOR BIOEQUIVALENCE STUDY

### Objective:

The primary objective of this study is to evaluate the bioequivalence of morphine and pramipexole in comparison to reference drugs. The study will focus on two critical pharmacokinetic parameters: the maximum plasma concentration ( $C_{max}$ ) and the area under the concentration-time curve (AUC). Demonstrating bioequivalence in these parameters is essential to establish that the test drug performs similarly to the reference drug in terms of absorption and overall exposure.

Historical data shows that morphine has an expected variability higher than that of pramipexole. Patient number will be determined using existing morphine pK data (PMID: 36331670).

The study will generate data for both female and male participants.

### Endpoints:

The primary endpoints for assessing bioequivalence are:

$C_{max}$ : The maximum observed concentration of the drug in plasma.

AUC: The area under the plasma concentration-time curve, which reflects the total drug exposure over time.

These parameters are standard in bioequivalence studies, as they provide comprehensive measures of the drug's absorption profile and systemic exposure.

### Assumptions and Input Parameters:

For the purpose of sample size determination and power analysis, the following assumptions are made based on prior data:

Expected Mean  $C_{max}$ : The mean  $C_{max}$  for morphine is expected to be of 7.7 ng/mL, with a standard deviation of 2.7 ng/mL.

Expected Mean AUC: The mean AUC for morphine is expected to be 40.7 ng·h/mL, with a standard deviation of 13.5 ng·h/mL.

Expected Difference: The difference between the test and reference drugs in terms of  $C_{max}$  and AUC is assumed to be zero, as the goal is to demonstrate bioequivalence.

Significance Level (Alpha): The study uses a two-sided significance level of 0.05.

Desired Power: To ensure the study has sufficient sensitivity to detect bioequivalence, a power of 80% is targeted.

Bioequivalence Margins: The accepted bioequivalence range is set between 80% and 125% for the ratio of  $C_{max}$  and AUC between the test and reference drugs. This range is consistent with regulatory standards and reflects the maximum allowable difference for the test drug to be considered equivalent to the reference drug.

### Sample Size Calculation:

The power analysis was conducted independently for both  $C_{max}$  and AUC to determine the number of participants needed to meet the study's objectives. The analysis revealed the following:

For  $C_{max}$ , the required sample size is 5 participants, given the expected variability (standard deviation of 2.7 ng/mL) and the targeted power of 80%.

For AUC, the required sample size is slightly smaller at 4 participants, due to the lower variability relative to the mean (standard deviation of 13.5 ng·h/mL).

Since the sample size must be adequate for both primary endpoints, the larger sample size of 5 participants will be used to ensure the study is adequately powered. To account for potential patient dropout, six males and six females will be recruited to the study.

#### Statistical Analysis:

The primary statistical analysis will involve calculating the 90% confidence intervals for the ratios of C<sub>max</sub> and AUC between the test and reference drugs. Bioequivalence will be concluded if these confidence intervals fall within the predefined margins of 80% to 125%. This approach aligns with regulatory guidelines and provides a rigorous test of whether the test drug can be considered bioequivalent to the reference.

#### Statistical Tests:

To compare the C<sub>max</sub> and AUC parameters between the test and reference drugs, a paired t-test will be employed, as the study follows a crossover design where each participant serves as their own control. The logarithmic transformation of C<sub>max</sub> and AUC values will be performed prior to analysis to stabilize variance and approximate normal distribution. The differences in the log-transformed values between the test and reference drugs will then be analyzed using the paired t-test. The results will be back-transformed to obtain the geometric mean ratios, and the corresponding 90% confidence intervals will be calculated. If these intervals lie entirely within the bioequivalence range of 80% to 125%, bioequivalence will be established.

## IND STATUS

As a key part of this FastTrack proposal, we will submit an IND that will be cleared for approval by the FDA to allow the Phase 1 human clinical trial to confirm PK, safety and tolerability.

**FDA Engagement:** A pre-IND meeting was held with the FDA on December 1, 2022 under PIND number 162905. The FDA has approved Amalgent to follow the 505(b)(2) regulatory pathway for the development program and has confirmed the scope of the clinical study protocol as proposed in this FastTrack application. In the issued meeting minutes, the FDA has approved the use of the listed drugs (LDs) of MS Contin (morphine sulfate ER tablet) under NDA 019516 and pramipexole under ANDA 090781 product 0.25 mg dihydrochloride tablet as the comparator in our planned PK study.

**Availability of the Study Agents:** Study agents will be prepared for trial use as part of this FastTrack project (see Research Strategy and Milestone Plan).

**CRO Engagement:** In preparation of the IND Amalgent has contracted with Allucent, a CRO who has managed and successfully cleared many hundreds of IND submissions. Allucent will handle the creation and finalization of various sections of the Investigational New Drug (IND) application. This includes authoring and refining key documents such as Form FDA 1571, Form FDA 3674, and the Cover Letter, all of which will be reviewed to Amalgent for review and approval prior to finalization. Allucent will also prepare the Investigator's Brochure and the different modules of the IND, covering regulatory, clinical, nonclinical, and chemistry, manufacturing, and controls (CMC) aspects. Each document will be crafted, reviewed, and finalized according to FDA guidelines, so that all materials and the total package is submission-ready. Allucent will generate the Clinical Study Report (CSR). The compilation of appendices, including subject data listings and other relevant documents, will be completed, ensuring that the final CSR is well-organized and linked to the necessary data. Throughout the project, Allucent will ensure that all deliverables are completed within the agreed timelines, maintaining a high standard of quality and regulatory compliance, and shall be overseen by the principal investigator for this project.

## **DISSEMINATION PLAN**

We will follow the “4.1.3.1 NIH Policy on Dissemination of NIH-Funded Clinical Trial Information” in the dissemination of data and other information pertaining to the proposed clinical trial. Following a grant award for the proposed Phase 1 clinical trial to determine the pharmacokinetics, tolerability, and safety for AMGT-0220, PPD, the clinical research organization running the study, will register the study with ClinicalTrials.gov no later than 21 calendar days after the enrollment of the first patient, in accordance with NIH policy (NOT-OD-16-149). Informed consent documents provided for patients will include disclosure of the trial on ClinicalTrials.gov. The study will be performed at PPD's Austin Clinical Research Unit. This site has internal policies that ensure that clinical trials for which they are a participant are registered with ClinicalTrials.gov, and that the results of the trial are submitted no later than one year after the primary completion date of the trial, in compliance with NIH policy (NOT-OD-16-149).

**Delayed Onset Studies**

| <b>Delayed<br/>Onset Study#</b>                  | <b>Study Title</b> | <b>Anticipated Clinical<br/>Trial?</b> | <b>Justification</b> |
|--|--------------------|--|----------------------|
| The form does not have any delayed onset studies |                    |  |                      |

## LITERATURE CITED

1. U.S. Overdose Deaths Decrease in 2023, First Time Since 2018 [Internet]. National Center for Health Statistics: Centers for Disease Control and Prevention; 2024 May. Available from: [https://www.cdc.gov/nchs/pressroom/nchs\\_press\\_releases/2024/20240515.htm#:~:text=Provisional%20data%20from%20CDC's%20National,drug%20overdose%20deaths%20since%202018](https://www.cdc.gov/nchs/pressroom/nchs_press_releases/2024/20240515.htm#:~:text=Provisional%20data%20from%20CDC's%20National,drug%20overdose%20deaths%20since%202018).
2. Keeler BE, Baran CA, Brewer KL, Clemens S. Increased excitability of spinal pain reflexes and altered frequency-dependent modulation in the dopamine D3-receptor knockout mouse. *Experimental Neurology*. 2012 Dec;238(2):273–283.
3. Brewer KL, Baran CA, Whitfield BR, Jensen AM, Clemens S. Dopamine D3 receptor dysfunction prevents anti-nociceptive effects of morphine in the spinal cord. *Front Neural Circuits*. 2014;8:62. PMCID: PMC4052813
4. Rodgers HM, Yow J, Evans E, Clemens S, Brewer KL. Dopamine D1 and D3 receptor modulators restore morphine analgesia and prevent opioid preference in a model of neuropathic pain. *Neuroscience*. 2019 May;406:376–388.
5. Samir S, Yllanes AP, Lallemand P, Brewer KL, Clemens S. Morphine responsiveness to thermal pain stimuli is aging-associated and mediated by dopamine D1 and D3 receptor interactions. *Neuroscience*. 2017 May;349:87–97.
6. Rodgers HM, Lim SA, Yow J, Dinkins ML, Patton R, Clemens S, Brewer KL. Dopamine D1 or D3 receptor modulators prevent morphine tolerance and reduce opioid withdrawal symptoms. *Pharmacol Biochem Behav*. 2020 Jul;194:172935. PMID: 32335101
7. Global opioids market to reach \$22.38 billion by 2026: Allied Market Research. EIN Presswire [Internet]. 2021 Dec 30; Available from: <https://www.einpresswire.com/article/559495079/global-opioids-market-to-reach-22-38-billion-by-2026-allied-market-research>
8. Passik SD. Issues in Long-term Opioid Therapy: Unmet Needs, Risks, and Solutions. *Mayo Clinic Proceedings*. 2009 Jul;84(7):593–601.
9. Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022. *MMWR Recomm Rep*. 2022 Nov 4;71(3):1–95.
10. Brat GA, Agniel D, Beam A, Yorkgitis B, Bicket M, Homer M, Fox KP, Knecht DB, McMahill-Walraven CN, Palmer N, Kohane I. Postsurgical prescriptions for opioid naive patients and association with overdose and misuse: retrospective cohort study. *BMJ*. 2018 Jan 17;j5790.
11. Fujii MH, Hodges AC, Russell RL, Roensch K, Beynnon B, Ahern TP, Holoch P, Moore JS, Ames SE, MacLean CD. Post-Discharge Opioid Prescribing and Use after Common Surgical Procedure. *J Am Coll Surg*. 2018 Jun;226(6):1004–1012. PMCID: PMC5971152
12. Nooromid MJ, Blay E, Holl JL, Bilimoria KY, Johnson JK, Eskandari MK, Stulberg JJ. Discharge prescription patterns of opioid and nonopioid analgesics after common surgical procedures. *Pain Rep*. 2018 Jan;3(1):e637. PMCID: PMC5802324
13. Opioid Use Disorder [Internet]. American Psychiatric Association. 2022. Available from: <https://www.psychiatry.org/patients-families/opioid-use-disorder>
14. Dydyk AM, Jain NK, Gupta M. Opioid Use Disorder. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 May 24]. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK553166/> PMID: 31985959
15. Taylor, NP. Vertex's pain prospect hits main goal in phase 3 trials but fails to beat Vicodin. *Fierce Biotech* [Internet]. 2024 Jan 30; Available from: <https://www.fiercebiotech.com/biotech/vertexs-pain-prospect-hits-main-goal-phase-3-trials-vicodin-comparison-complicates-picture>
16. Lachiewicz PF, Lee GC, Pollak RA, Leiman DG, Hu J, Sah AP. HTX-011 Reduced Pain and Opioid Use After Primary Total Knee Arthroplasty: Results of a Randomized Phase 2b Trial. *The Journal of Arthroplasty*. 2020 Oct;35(10):2843–2851.
17. Patton R, Mainhart A, Clemens S, Brewer K. Pramipexole Improves the Analgesic Properties of Low-dose Morphine in the Treatment of Acute Pain (S9.002). *Neurology*. 2022 May 3;98(18\_supplement):1198.
18. Corder G, Castro DC, Bruchas MR, Scherrer G. Endogenous and Exogenous Opioids in Pain. *Annu Rev Neurosci*. 2018 Jul 8;41(1):453–473.

19. Kieffer BL, Evans CJ. Opioid Tolerance—In Search of the Holy Grail. *Cell*. 2002 Mar;108(5):587–590.
20. Clemens S, Belin-Rauscent A, Simmers J, Combes D. Opposing modulatory effects of D1- and D2-like receptor activation on a spinal central pattern generator. *J Neurophysiol*. 2012 Apr;107(8):2250–2259. PMID: 22262823
21. Carter M, Shieh J. Animal Behavior. Guide to Research Techniques in Neuroscience [Internet]. Elsevier; 2015 [cited 2024 Aug 4]. p. 39–71. Available from: <https://linkinghub.elsevier.com/retrieve/pii/B9780128005118000022>
22. Mendifto E, Orlando V, De Rosa G, Minghetti P, Musazzi U, Cahir C, Kurczewska-Michalak M, Kardas P, Costa E, Sousa Lobo J, Almeida I. Patient Centric Pharmaceutical Drug Product Design—The Impact on Medication Adherence. *Pharmaceutics*. 2020 Jan 3;12(1):44.
23. Guideline on clinical development of fixed combination medicinal products [Internet]. European Medicines Agency; 2017 Mar. Available from: [https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-development-fixed-combination-medicinal-products-revision-2\\_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-development-fixed-combination-medicinal-products-revision-2_en.pdf)
24. Kieburtz K. Safety and efficacy of pramipexole in early Parkinson disease. A randomized dose-ranging study. *Parkinson Study Group*. *JAMA: The Journal of the American Medical Association*. 1997 Jul 9;278(2):125–130.
25. Winkelman JW, Sethi KD, Kushida CA, Becker PM, Koester J, Cappola JJ, Reess J. Efficacy and safety of pramipexole in restless legs syndrome. *Neurology*. 2006 Sep 26;67(6):1034–1039.
26. Shen T, Ye R, Zhang B. Efficacy and safety of pramipexole extended-release in Parkinson's disease: a review based on meta-analysis of randomized controlled trials. *Euro J of Neurology*. 2017 Jun;24(6):835–843.
27. Bostwick JM, Hecksel KA, Stevens SR, Bower JH, Ahlskog JE. Frequency of New-Onset Pathologic Compulsive Gambling or Hypersexuality After Drug Treatment of Idiopathic Parkinson Disease. *Mayo Clinic Proceedings*. 2009 Apr;84(4):310–316.
28. Dodd ML, Klos KJ, Bower JH, Geda YE, Josephs KA, Ahlskog JE. Pathological Gambling Caused by Drugs Used to Treat Parkinson Disease. *Arch Neurol*. 2005 Sep 1;62(9):1377.
29. You ZB, Bi GH, Galaj E, Kumar V, Cao J, Gadiano A, Rais R, Slusher BS, Gardner EL, Xi ZX, Newman AH. Dopamine D3R antagonist VK4-116 attenuates oxycodone self-administration and reinstatement without compromising its antinociceptive effects. *Neuropsychopharmacol*. 2019 Jul;44(8):1415–1424.
30. Prescribing information for MIRAPEX (pramipexole dihydrochloride tablets), for oral use [Internet]. Ridgefield, CT: Boehringer Ingelheim; 2021. Report No.: NDA 020667. Available from: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2008/020667s014s017s018lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/020667s014s017s018lbl.pdf)
31. Prescribing information for MS CONTIN (morphine sulfate extended-release tablets), for oral use CII [Internet]. Stamford, CT: Purdue Pharma L.P.; 2021. Report No.: NDA 019516. Available from: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2010/019516s034lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/019516s034lbl.pdf)
32. Sakurai A, Wakuda T, Yoshida R, Katoh S, Yamasue H. Successful discontinuation of oxycodone under pramipexole treatment for restless legs syndrome due to withdrawal. *Psychiatry Clin Neurosci*. 2021 Mar;75(3):112–113.
33. Naeem M, Mahmood A, Khan S, Shahiq Z. Development and Evaluation of Controlled-Release Bilayer Tablets Containing Microencapsulated Tramadol and Acetaminophen. *Trop J Pharm Res* [Internet]. 2010 Sep 2 [cited 2024 Aug 15];9(4). Available from: <http://www.ajol.info/index.php/tjpr/article/view/58926>
34. QUALITY RISK MANAGEMENT Q9(R1) [Internet]. INTERNATIONAL COUNCIL FOR HARMONISATION; 2023 Jan. Available from: [https://database.ich.org/sites/default/files/ICH\\_Q9%28R1%29\\_Guide-line\\_Step4\\_2023\\_0126\\_0.pdf](https://database.ich.org/sites/default/files/ICH_Q9%28R1%29_Guide-line_Step4_2023_0126_0.pdf)
35. Q9(R1) Quality Risk Management [Internet]. Federal Drug Administration; 2023 May. Available from: <https://www.fda.gov/media/167721/download>
36. Atrux-Tallau N, Naimi Z, Jaudinot EO. Pharmacokinetics of Morphine Sulfate Orosoluble Tablets and Bioequivalence with Immediate-Release Oral Morphine Sulfate Formulations in Healthy Adult Subjects Under Fasting Conditions: Single-Dose Comparative Bioavailability Studies. *Clin Drug Investig*. 2022 Dec;42(12):1101–1112. PMCID: PMC9705466

## COMMERCIALIZATION PLAN LITERATURE CITED

1. Patton, R., Mainhart, A., Clemens, S. & Brewer, K. Pramipexole Improves the Analgesic Properties of Low-dose Morphine in the Treatment of Acute Pain (S9.002). *Neurology* **98**, 1198 (2022).
2. Rodgers, H. M. *et al.* Dopamine D1 or D3 receptor modulators prevent morphine tolerance and reduce opioid withdrawal symptoms. *Pharmacol. Biochem. Behav.* **194**, 172935 (2020).
3. Key Substance Use and Mental Health Indicators in the United States: Results from the 2015 National Survey on Drug Use and Health | CBHSQ Data. <https://www.samhsa.gov/data/report/key-substance-use-and-mental-health-indicators-united-states-results-2015-national-survey>.
4. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. (American Psychiatric Publishing, 2013).
5. Boslett, A. J., Denham, A. & Hill, E. L. Using contributing causes of death improves prediction of opioid involvement in unclassified drug overdoses in US death records. *Addiction* **115**, 1308–1317 (2020).
6. Abuse, N. I. on D. Drug Overdose Death Rates | National Institute on Drug Abuse (NIDA). <https://nida.nih.gov/research-topics/trends-statistics/overdose-death-rates> (2024).
7. Ruhm, C. J. Corrected US opioid-involved drug poisoning deaths and mortality rates, 1999–2015. *Addiction* **113**, 1339–1344 (2018).
8. Jones, C. M., Han, B., Baldwin, G. T., Einstein, E. B. & Compton, W. M. Use of Medication for Opioid Use Disorder Among Adults With Past-Year Opioid Use Disorder in the US, 2021. *JAMA Netw. Open* **6**, e2327488 (2023).
9. U.S. Overdose Deaths Decrease in 2023, First Time Since 2018. [https://www.cdc.gov/nchs/pressroom/nchs\\_press\\_releases/2024/20240515.htm](https://www.cdc.gov/nchs/pressroom/nchs_press_releases/2024/20240515.htm) (2024).
10. Luo, F. State-Level Economic Costs of Opioid Use Disorder and Fatal Opioid Overdose — United States, 2017. *MMWR Morb. Mortal. Wkly. Rep.* **70**, (2021).
11. Florence, C., Luo, F. & Rice, K. The economic burden of opioid use disorder and fatal opioid overdose in the United States, 2017. *Drug Alcohol Depend.* **218**, 108350 (2021).
12. Coyle, D. T. *et al.* Opioid analgesic dose and the risk of misuse, overdose, and death: A narrative review. *Pharmacoepidemiol. Drug Saf.* **27**, 464–472 (2018).
13. Dowell, D. CDC Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022. *MMWR Recomm. Rep.* **71**, (2022).
14. Vertex Announces Positive Results From the VX-548 Phase 3 Program for the Treatment of Moderate-to-Severe Acute Pain | Vertex Pharmaceuticals Newsroom. <https://news.vrtx.com/news-releases/news-release-details/vertex-announces-positive-results-vx-548-phase-3-program>.
15. Lachiewicz, P. F. *et al.* HTX-011 Reduced Pain and Opioid Use After Primary Total Knee Arthroplasty: Results of a Randomized Phase 2b Trial. *J. Arthroplasty* **35**, 2843–2851 (2020).
16. Hall, M. J., Schwartzman, A., Zhang, J. & Liu, X. Ambulatory Surgery Data From Hospitals and Ambulatory Surgery Centers: United States, 2010. *Natl. Health Stat. Rep.* 1–15 (2017).
17. Brat, G. A. *et al.* Postsurgical prescriptions for opioid naive patients and association with overdose and misuse: retrospective cohort study. *BMJ* **360**, j5790 (2018).
18. Rui, P. & Schappert, S. M. Opioids Prescribed at Discharge or Given During Emergency Department Visits Among Adults in the United States, 2016. *NCHS Data Brief* 1–8 (2019).
19. Products - Data Briefs - Number 461 - January 2023. <https://www.cdc.gov/nchs/products/databriefs/db461.htm> (2023) doi:10.15620/cdc:122879.
20. Zelaya, C. E., Dahlhamer, J. M., Lucas, J. W. & Connor, E. M. Chronic Pain and High-impact Chronic Pain Among U.S. Adults, 2019. *NCHS Data Brief* 1–8 (2020).
21. Rikard, S. M. Chronic Pain Among Adults — United States, 2019–2021. *MMWR Morb. Mortal. Wkly. Rep.* **72**, (2023).
22. Lawal, O. D. *et al.* Rate and Risk Factors Associated With Prolonged Opioid Use After Surgery: A Systematic Review and Meta-analysis. *JAMA Netw. Open* **3**, e207367 (2020).
23. Vowles, K. E. *et al.* Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. *Pain* **156**, 569–576 (2015).

24. Thomas, K. H. *et al.* Prevalence of problematic pharmaceutical opioid use in patients with chronic non-cancer pain: A systematic review and meta-analysis. *Addict. Abingdon Engl.* (2024) doi:10.1111/add.16616.
25. Products - Vital Statistics Rapid Release - Provisional Drug Overdose Data. <https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm> (2024).
26. Daoust, R. *et al.* Side effects from opioids used for acute pain after emergency department discharge. *Am. J. Emerg. Med.* **38**, 695–701 (2020).
27. Opioids Market Size, Share & Growth Analysis Report, 2030. <https://www.grandviewresearch.com/industry-analysis/opioids-market>.



August 26<sup>th</sup>, 2024

Malcolm Meyn, PhD  
Chief Scientific Officer  
Amalgent Therapeutics  
300 E First St  
Greenville, NC, 27858

Dear Malcolm,

I am writing this letter in strong and unwavering support of Amalgent Therapeutics' SBIR application titled, "First Clinical Development of a Novel Fixed Dose Combination Pain Therapeutic with Decreased Potential for Abuse and Tolerance." Successfully completing this project will represent a major breakthrough in tackling the pressing issues surrounding opioid use in pain management, particularly reducing the risks of opioid use disorder (OUD) and the development of opioid tolerance.

Throughout my career as an Emergency Medicine Physician and most recently at ECU Health Medical Center, I have been deeply involved in the acute management of pain, often requiring the judicious use of opioids. **My extensive experience in emergency care has afforded me a comprehensive understanding of the urgent need for safer, more effective pain management options.** This has included developing and implementing protocols that prioritize non-opioid alternatives to reduce the potential for opioid misuse and addiction in high-pressure clinical settings.

Drawing on my hands-on experience with pain management in such environments, I can say that AMGT-0220 holds high promise for a clinically relevant, safe and efficacious therapy to treat acute pain. This drug, which combines pramipexole with low-dose morphine, offers a novel therapeutic approach that could significantly improve pain management practices. **By reducing the risks of opioid dependence and tolerance, while removing the risk of addiction, AMGT-0220 holds great promise, particularly in acute care settings where the need for rapid and effective pain relief is critically important.**

My strong belief in the promise of Amalgent Therapeutics is not just professional but also personal. As an investor in the company, I am confident that the innovative approaches being developed will have a profound and positive impact on the field of pain therapeutics, offering safer and more effective options for patients. The potential of AMGT-0220 to change the landscape of opioid therapy, by addressing both pain and the associated risks of traditional opioid treatments, is a significant and necessary advancement.

I fully support Amalgent Therapeutics in your efforts and look forward to hearing about a favorable funding decision for this vital project and am eager to see the development of a safer, more effective pain management therapy that can reshape how we approach pain relief in an acute setting.

I am excited about the impact this project will have in improving patient outcomes in pain management.

Sincerely,

A handwritten signature in black ink that reads "G. Kirk Jones".

G. Kirk Jones, MD, FACEP  
Dept. of Emergency Medicine  
Brody School of Medicine & ECU Health Medical Center  
Greenville, NC 27834

# Tyler LaCoste, PA-C

EMERGENCY MEDICINE  
PHYSICIAN ASSOCIATE

08/15/2024

Malcolm Meyn, PhD  
Chief Scientific Officer  
Amalgent Therapeutics  
300 E First St  
Greenville, NC, 27858

Dear Malcolm,

I am writing this letter to support Amalgent Therapeutics' proposal to be submitted to the NIH's SBIR program. I am an Emergency Medicine Physician Associate with extensive experience in managing acute and chronic pain management in opioid-naïve and non-naïve patients in emergency department (ED).

Pain is the most prevalent symptom prompting emergency department (ED) visits, with opioids often being the primary choice for analgesic treatment. While multimodal analgesic strategies that prioritize patient safety and clinical efficacy are utilized, in my experience, morphine is the most commonly used course of pain management using an opioid in the ED. This is due to morphine being the cost effective and well tolerated among opioid-naïve patients. For patients who are not opioid-naïve, effective pain management may necessitate higher doses of morphine or escalation to more potent opioids such as fentanyl. Unfortunately, most emergencies require prolonged usage of opioids (both inpatient and outpatient) which substantially increases the risk of developing tolerance, dependence, and addiction over time.

Amalgent Therapeutics is proposing a novel approach to pain management that directly addresses the critical issues surrounding opioid use, particularly in emergency medicine settings. Their development of a drug, which combines low-dose morphine with pramipexole, promises to mitigate the risks of opioid tolerance and dependency—common and serious concerns in our field. This initiative not only aligns with current needs for safer opioid therapies but also introduces a potential improvement to the standard of care in pain management.

I am fully confident in Amalgent Therapeutics' ability to deliver this innovative product swiftly and effectively. Their strategy is firmly rooted in comprehensive preclinical research and smartly utilizes existing FDA-approved drugs, which enhances safety and accelerates regulatory approval. This approach ensures that the product can be quickly integrated into clinical settings, providing a much-needed solution in the pain management domain much sooner than completely new therapeutics that require extensive testing and approval processes. The potential of this product to transform current pain management practices significantly is substantial, guaranteeing its relevance and marketability in both emergency and in chronic care settings.

I fully support Amalgent Therapeutics and their endeavors to provide an improved therapeutic approach for managing moderate to severe pain. I look forward to being kept apprised of your developments.

Sincerely,



Tyler LaCoste, PA-C  
Emergency Medicine Physician Associate  
Denver, CO

**SIGNAL HILL ADVISORS**

August 26, 2024

Malcolm Meyn, PhD  
Chief Scientific Officer  
Amalgent Therapeutics  
300 E First St  
Greenville, NC, 27858

Dear Malcolm,

I am pleased to provide my full and enthusiastic support for my role as the strategic advisor in Amalgent Therapeutics' SBIR application entitled, "First Clinical Development of a Novel Fixed Dose Combination Pain Therapeutic with Decreased Potential for Abuse and Tolerance." This innovative project aims to address critical challenges associated with opioid use in pain management, a cause I am deeply committed to supporting.

Throughout my 30-year career in the pharmaceutical, biotech, and medical device industries, I have had the privilege of leading transformative efforts at several major organizations, including Mallinckrodt, TEVA Pharmaceuticals, M2GEN, and MiMedx. My experience spans the full spectrum of drug development, from early-stage R&D to successful product launches and global market expansion. I have been instrumental in overseeing strategic initiatives that have resulted in FDA approvals, successful mergers and acquisitions, and significant capital raises, such as the \$150 million raised during my tenure at MiMedx that including a NASDAQ registration in 2020.

My role as a strategic advisor to Amalgent Therapeutics is to provide oversight and guidance in the execution of this project, particularly in navigating the product landscape and preparing for the first-in-human clinical trials of AMGT-0220. The combination of low-dose morphine with pramipexole, both of which are FDA-approved drugs, offers a promising therapeutic option that addresses the urgent need for safer pain management solutions. I will contribute my expertise in product strategy, strategic planning, and clinical trial design to ensure that Amalgent meets all the necessary milestones for this project, from IND submission to the successful completion of the Phase 1 trial.

My fee for these advisory services is \$5,000, covering my efforts during the proposal phase. I am fully committed to supporting Amalgent Therapeutics in this critical endeavor and believe that AMGT-0220 has the potential to make a significant impact on the opioid crisis by providing an alternative that reduces the risk of addiction and tolerance.

I look forward to our continued collaboration and wish you the best of luck in securing the necessary funding for this important project.

Sincerely,



Timothy R. Wright  
Chief Executive Officer  
Phone: 617-678-7607



August 26, 2024

Malcolm Meyn, PhD  
Chief Scientific Officer  
Amalgent Therapeutics  
300 E First St  
Greenville, NC, 27858

Dear Malcolm,

I am writing to confirm my role as the clinical consultant in Amalgent Therapeutics' SBIR application titled "First Clinical Development of a Novel Fixed Dose Combination Pain Therapeutic with Decreased Potential for Abuse and Tolerance." This initiative is a critical advancement in addressing the opioid crisis by developing safer and more effective pain management therapies.

With over three decades of experience in the pharmaceutical and biotechnological fields, my expertise spans clinical development, medical affairs, and the successful oversight of numerous clinical trials. My career includes serving as Senior Vice President for Quintiles/IQVIA, Chief Medical Officer for various companies, such as Oxygen Biotherapeutics, Talecris/Grifols, and Entera Health, where I have led efforts in the development of therapies for neurological, psychiatric, and pain-related disorders. My extensive experience in pain management includes work on treatments for dental pain, migraine, central pain syndrome, and neuropathic pain, making me particularly well-suited to guide the clinical aspects of Amalgent's innovative project.

In this consulting role, I will provide oversight and strategic input on the clinical development of AMGT-0220, a novel combination of pramipexole and low-dose morphine designed to offer effective pain relief while minimizing the risk of opioid use disorder and tolerance. This project not only holds promise for significant clinical benefits but also expedites the regulatory approval process via the 505(b)2 pathway, as outlined in Amalgent's development plan.

My consultant fee is \$7,500 per year, covering my contributions during the proposal phase, including reviewing clinical protocols, patient-specific outcomes, and ensuring the adherence to regulatory requirements. I am fully committed to supporting Amalgent Therapeutics as we prepare for the first-in-human trials and work towards the commercialization of this important therapeutic.

I look forward to our continued collaboration and am confident that our combined efforts will bring significant advancements in pain management, providing new hope for patients and potentially changing the landscape of opioid therapy.

Sincerely,

A handwritten signature in black ink, appearing to read "Gerald L. Klein".

Gerald L. Klein, M.D.  
Chief Medical Officer  
Amalgent Therapeutics  
Phone: 919-930-9180



August 27, 2024

Malcolm Meyn, PhD  
Chief Scientific Officer  
Amalgent Therapeutics  
300 E First St  
Greenville, NC, 27858

Dear Malcolm,

I am writing this letter to express my unqualified support for Amalgent Therapeutics' SBIR application entitled, "First Clinical Development of a Novel Fixed Dose Combination Pain Therapeutic with Decreased Potential for Abuse and Tolerance" and to confirm my role as a consultant for the project. When completed, this project will be a big leap forward in addressing the critical challenges associated with opioid use in pain management, particularly in mitigating the risks of opioid use disorder (OUD) and opioid tolerance.

As a Professor of Neurology and the Director of the Comprehensive Pain Center at Albany Medical Center, I have dedicated my career to advancing the understanding and treatment of chronic pain. My role as a consultant in this project will leverage my extensive expertise in pain management, opioid pharmacology, and clinical research, which includes leading numerous clinical trials focused on innovative pain therapies.

My background includes over three decades of experience in the neurology and pain management fields, during which I have contributed to the development and implementation of novel therapeutic approaches. My work at Albany Medical Center has involved overseeing a range of clinical studies, including trials on opioid-induced constipation, neuropathic pain, and various pain management strategies. Additionally, I have served as the Vice Chair of the Department of Neurology and directed the Pain Management Fellowship, where I have been instrumental in educating the next generation of pain specialists.

In this consulting role, I will provide expert guidance on the clinical development of AMGT-0220, particularly in reviewing patient-specific outcomes and potential adverse effects. The combination of pramipexole with low-dose morphine presents a unique therapeutic approach that has the potential to significantly impact the field of pain management by reducing the risk of opioid dependence and tolerance.

My consultant fee is \$5,000 for the duration of this proposal phase, reflecting my commitment to contributing my expertise to this promising and innovative project. I fully support Amalgent Therapeutics in your efforts to secure funding and develop a safer, more effective pain management therapy.

I look forward to our continued collaboration and am confident that this project will achieve significant milestones in improving patient outcomes in pain management.

Sincerely,

A handwritten signature in black ink that reads 'Charles E. Argoff'.

Charles E. Argoff, M.D.  
Professor of Neurology, Vice Chair, Department of Neurology  
Director, Comprehensive Pain Center, Director, Pain Management Fellowship  
Albany Medical Center  
47 New Scotland Avenue, Albany, NY 12208  
Phone: (516) 456-0222



7302 Golden Star Lane, Carlsbad, CA 92011  
Phone: 760-846-6763 Fax: 760-814-2202  
[www.kellystatisticalconsulting.com](http://www.kellystatisticalconsulting.com)

Malcolm A. Meyn PhD, MSHS  
Chief Scientific Officer  
Amalgent Therapeutics, Inc.  
300 East First St.  
Greenville, NC 27858

August 29, 2024

Dear Dr. Meyn,

I would be delighted to act as a statistical consultant for your NIH Fast-Track Grant application titled, "Clinical Development of the First Fixed Dose Combination Pain Therapeutic with Decreased Potential for Abuse and Tolerance", which will be considered for Small Business Innovation Research (SBIR) funding. I am an Accredited Professional Statistician™ and have over 25 years of experience in statistical consulting and data analysis for observational studies, clinical trials and preclinical experiments. I have designed studies, analyzed data, written statistical analysis plans and reports in the oncology, pharmaceutical, vaccine, medical device and diagnostics arenas.

I served in both industry and academic settings in a wide variety of subject areas. In my former position as an Associate Professor of Statistics at San Diego State University, I co-founded and co-directed the university's statistical consulting center. In my current position as the President of Kelly Statistical Consulting, I lead a team of experienced M.S.-degree biostatisticians, who are trained in statistical methodology and skilled in statistical programming. We assist clients in designing powerful and effective clinical trials, writing statistical analysis plans, analyzing data and submitting new drug applications, pre- market approvals, 510(k) clearances and product development protocols to the FDA.

I feel that my core strength in performing statistical data analyses for multi-center studies and randomized controlled trials will be a great added value to your proposed studies. Specifically, for the Phase 1 pK clinical study, I will provide biostatistician support during study design and planning; and will perform the final biostatistical analyses for primary and secondary endpoints, including management of missing data. My fee is \$5,000 per year for the duration of the Phase II portion of the SBIR.

Sincerely,

A handwritten signature in black ink, appearing to read 'Colleen Kelly'.

Colleen Kelly, Ph.D., PStat  
Principal Statistician and President  
Kelly Statistical Consulting  
Email: [ckelly@kellystatisticalconsulting.com](mailto:ckelly@kellystatisticalconsulting.com)

## **RESOURCE SHARING PLAN**

The proposed scope of work will not result in the production of (1) unique model organism research resources and/or (2) unique research tools as defined by the NIH in their guidance documents entitled "Model Organisms Sharing Policy" and "Research Tools Policy" available on the NIH website

Consistent with Bayh-Dole Regulations, Amalgent Therapeutics is committed to the timely development of a commercial product with support from the NIH SBIR/STTR funding mechanism. Commercialization of AMGT-0220, an effective low-dose morphine pain medication, will lead to its broad dissemination and use by the research community and the general public, thereby enhancing the value of NIH-sponsored research.

Amalgent Therapeutics will make the non-proprietary results and accomplishments of the research available to the research community and the public at large by the timely release and sharing of data. Following the completion of actions needed to protect intellectual property, Amalgent Therapeutics will seek to publish the original research in primary scientific journals. They will assert copyright in scientific and technical articles based on data produced under the grant where necessary. For each publication that results from the grant-supported research, we will include an acknowledgment of NIH grant support and follow guidelines regarding free access to published materials. Information on each publication resulting from work performed under the NIH grant-supported project will be included in the annual and/or final progress report submitted to the NIH awarding office. Proprietary developments will be protected using intellectual property rights.

## ***INTELLECTUAL PROPERTY RIGHTS***

Amalgent Therapeutics will assert copyright in scientific and technical articles based on data produced under the grant where necessary, but we will also make every effort to keep technologies developed as a result of this research project widely available and accessible to the research community. If additional patents are filed and the technology licensed, we will only seek exclusivity in cases where this approach is determined to be the best route for successful development of the technology for public use and benefit.

NIH Generated message:

The Other Plan(s) attachment included with the application is not evaluated during the peer review process but will be evaluated prior to a funding decision. Although part of the official submission, the attachment is maintained as a separate document in eRA Commons viewable by authorized users and is not part of this assembled application.

## AUTHENTICATION OF KEY BIOLOGICAL AND/OR CHEMICAL RESOURCES

### **Overview:**

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The proposed studies in Phase I will include key chemicals needed to prepare the clinical batch of AMGT-0220 for the Phase 1 clinical trial planned for Phase II.

#### **1. Specialty Chemicals**

All raw materials, reagents, solvents, and auxiliary chemicals required to manufacturing the clinical batch of AMGT-0220 will be purchased by Catalent. Commercially available materials will be released based on supplier CoA with a target purity of >98%.

The manufactured clinical batch of AMGT-0220 will be released based on yield, and purity (HPLC), identity (NMR/MS), color (appearance), gas chromatography (residual solvents), Karl Fischer titration (moisture), and microbial limit testing.

morphine sulfate (Hikma, NDA 022195; 15 mg) and pramipexole hydrochloride (ANDA 090781; 0.125 mg) will be purchased as clinical-grade material that has passed release specs.