



University of Pittsburgh

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# Use of Xtampza ER to overcome difficulties in swallowing opioid pills

**CLINICAL RESEARCH PROTOCOL**

DEPARTMENT OF ANESTHESIOLOGY

UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE

IRB PRO17040444

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## Table of Contents

<b>Study Information</b> .....	<b>3</b>
<b>Study Contacts</b> .....	<b>4</b>
<b>Subjects</b> .....	<b>4</b>
<b>Eligibility</b> .....	<b>5</b>
<b>Subject Groups/Treatment Arms</b> .....	<b>6</b>
Treatment Arm 1: Open Label .....	6
<b>Study Schedule</b> .....	<b>7</b>
<b>Overview of Schedule</b> .....	<b>7</b>
<b>Recruitment and Screening</b> .....	<b>7</b>
<b>Compensation Schedule</b> .....	<b>8</b>
<b>Detailed Study Schedule with Checklists</b> .....	<b>9</b>
Clinic Visit 1 .....	9
Clinic Visit 2 .....	9
Clinic Visit 3 .....	9
Clinic Visit 4 (End of Study) .....	10
Daily Texts .....	10
Weekly Surveys .....	10
<b>Study Measures</b> .....	<b>12</b>
Medical History.....	12
Medication Diary .....	12
Medication Satisfaction Questions.....	12
Modified Baylor Dysphagia Questionnaire .....	12
Pain Diary.....	13
Pill Swallowing Difficulty Questions .....	13
PROMIS-29 Adult Profile v2.0 (Participant Version).....	13
Text Message Compliance .....	14
Urine Pregnancy Test.....	14
Weekly Survey .....	14
<b>Text Message Scripts</b> .....	<b>15</b>
<b>Statistical Analysis Plan</b> .....	<b>16</b>
<b>Outcomes to be Analyzed</b> .....	<b>16</b>
Primary Outcome   Pain Intensity.....	16
<b>Overview of Analysis Plan</b> .....	<b>17</b>
<b>Data Management</b> .....	<b>17</b>
<b>Scripts and Files Needed</b> .....	<b>17</b>
<b>Updating Data Files</b> .....	<b>17</b>
<b>Mosio SMS Text Messaging System</b> .....	<b>19</b>
<b>Initial Set-up (at Clinic Visit 1)</b> .....	<b>19</b>
<b>Scheduling Appointment Reminders</b> .....	<b>20</b>
<b>Study Medication</b> .....	<b>18</b>
<b>Prescribing Xtampza ER</b> .....	<b>22</b>

## Study Information

### Principle

Investigator: Ajay Wasan, MD, MSc

Study Coordinators: Andrea G. Gillman, PhD

Institution: University of Pittsburgh School of Medicine  
Department of Anesthesiology

IRB Protocol: University of Pittsburgh PRO17040444  
Approved: 11/10/2017  
Expiration Date: 10/24/2018

Study Location: UPMC Pain Medicine Clinic at Centre Commons  
5750 Centre Ave, Ste. 400  
Pittsburgh, PA 15206

Sponsoring Agency: Collegium Pharmaceutical, Inc.  
780 Dedham Street, Suite 800  
Canton, MA 02021

Study Objective: Xtampza ER is an oral opioid medication capsule that can be opened to allow the pellets to be added to food or drink. This study will investigate whether Xtampza ER can adequately address common quality of care deficits of opioid medications.

Specific Aims: We hypothesize that the subjects in our study will report comparable pain relief and improved ability to take opioid medication through the dispersal of the microspheres in food or liquid.

1. The primary hypothesis is that there will be a significant improvement in ratings of swallowing difficulties in comparing pre- vs. post-administration scores.
2. The secondary hypothesis is that there will be a non-inferior difference between pre- and post-pain ratings. In other words, after being converted to Xtampza ER, there will be no reported meaningful differences in the degree of pain.

## Study Contacts

Principle Investigator	<p>Ajay D. Wasan, MD, MSc          Dept. of Anesthesiology, University of Pittsburgh School of Medicine          UPMC Pain Medicine          (412) 665-8048  <a href="mailto:wasanad@upmc.edu">wasanad@upmc.edu</a></p>
Study Coordinators	<p>Andrea G. Gillman, PhD          Dept. of Anesthesiology, University of Pittsburgh School of Medicine          (412) 665-2904  <a href="mailto:gillmana@pitt.edu">gillmana@pitt.edu</a></p>
Sponsoring Agency	<p>Michael DeGeorge, PharmD          VP, Medical Affairs          Collegium Pharmaceutical, Inc.          (631) 431-4507  <a href="mailto:mdegeorge@collegiumpharma.com">mdegeorge@collegiumpharma.com</a></p> <p>Danielle Ruch, MBA          Manager, Medical Operations          Collegium Pharmaceutical, Inc.          (781) 232-0770  <a href="mailto:druch@collegiumpharma.com">druch@collegiumpharma.com</a></p>
Pharmacy	<p>Howard Brenner          Avella of Orlando, Inc.          100 Technology Park, Suite 1525          Lake Mary, FL 32746          Phone: (407) 792-7099          Fax: (877) 430-4768  <a href="mailto:howard.brenner@avella.com">howard.brenner@avella.com</a></p>
Text Messaging	<p>Noel Chandler, CEO          Mosio Simple Support  <a href="mailto:noel@mosio.com">noel@mosio.com</a></p> <p>Charlotte Justice, Account Manager          Mosio Simple Support  <a href="mailto:charlotte@mosio.com">charlotte@mosio.com</a></p> <p>Jay Sachdev, Software Developer          Mosio Simple Support  <a href="mailto:jay@mosio.com">jay@mosio.com</a></p>

## Subjects

## Eligibility

- Inclusion Criteria:
1. Adult subjects must have noncancer chronic pain for at least six months on a daily basis,
  2. Be prescribed opioids on a daily basis
  3. Have an upper dose limit of daily opioids of 200 mg of morphine equivalents. This is because at doses greater than 200 mg daily, in our experience it is much more difficult to convert completely to another opioid compound within a week. Fentanyl and methadone users will not be specifically excluded unless their dosages fall outside this range.
  4. Ages 21-70
  5. Reported difficulty swallowing their opioid medication on the screening form at a level determined significant by the PI.
  6. Having a mobile phone. A smart phone is not required to respond to the text messages.
  7. Having Internet access to be able to respond to the emailed weekly surveys.
  8. If sexually active and able to become pregnant, must agree to use an acceptable method of birth control (hormonal methods, barrier methods with spermicide, intrauterine device (IUD) or abstinence).
  9. Only Pain Medicine Clinic patients may participate in this study

- Exclusion Criteria:
1. Inability to understand the surveys and complete them.
  2. Pregnancy
  3. High risk for opioid addiction and/or abuse behaviors
  4. Any condition, physical or mental, that in the investigator's judgment precludes optimal participation in the study procedures. This includes any documented current history of liver disease, renal insufficiency, delirium, alcohol use disorder, breast-feeding mothers, acute or severe asthma, COPD requiring home oxygen, GI obstruction, biliary tract disease, pancreatitis, cardiac arrhythmia, bladder or urethral obstruction, adrenal insufficiency, psychosis, or taking medications which are potent inhibitors of the CYP3A4 enzyme (such as protease inhibitors, macrolide antibiotics, or antifungals).
  5. Demonstration of abusive alcohol behavior. For women, this is more than 3 drinks on any single day or more than 7 drinks per week. For men, more than 4 drinks on any single day or more than 14 drinks per week.
  6. Currently taking fentanyl or methadone
  7. Exhibiting the following contradicted conditions: (1) significant respiratory depression (2) acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment (3) known or suspected gastrointestinal obstruction, including paralytic ileus (4) hypersensitivity (e.g. anaphylaxis) to oxycodone (5) patients with chronic pulmonary disease (6) elderly, cachet, or debilitated patients (7) patients with evidence of increased intracranial pressure, brain tumors, head injury, or impaired consciousness (8) patients with seizure disorders (9) pregnant and breastfeeding women, due to risks to the fetus/baby

## Subject Groups/Treatment Arms

### Treatment Arm 1: Open Label

Target Enrollment: 20

Description: Subjects will be prescribed Xtampza ER for the duration of the study. Dosage and side effects will be monitored by the PI.

Treatment Protocol: Administration of Xtampza ER will begin at Clinic Visit 2 in Week 2 of the study. During this clinic visit, subjects will discuss with the investigator conversion of their current opioids to Xtampza ER. If subjects are on a mix of short and long acting opioids, they may elect to only convert the long-acting opioid if this is the medication giving them the swallowing difficulties. In other words, ideally we would convert both the long and short acting opioids to Xtampza ER. However, we realize that subjects may prefer to still have their current breakthrough medication, which may not be giving them swallowing difficulties, and thus the accommodation of only converting the long-acting opioids. We will use a standard conversion table to calculate the dose. But, due to the phenomenon of incomplete cross tolerance, we will only convert 75% of the calculated dose to Xtampza ER. Subjects are dispensed a 7-10 day supply of Xtampza ER at the end of the visit. As per manufacturer recommendations, subjects will be instructed to take each dose of Xtampza ER with the same amount of food. Subjects will be instructed to open the capsules, sprinkle the microspheres onto soft food such as pudding or applesauce, and then consume the food.

# Study Schedule

## Overview of Schedule

Week 0:	Recruitment & Screening
Week 1:	Clinic Visit 1, Daily text messaging begins
Week 2:	Clinic Visit 2
Week 3:	Clinic Visit 3
Week 4:	Weekly Survey – Week 4
Week 5:	Weekly Survey – Week 5
Week 6:	End of Study. Clinic Visit 4, Daily text messaging ends

## Recruitment and Screening

**Recruitment:** Patients will be recruited from the UPMC Pain Medicine Clinic at Centre Commons from the PI and clinic providers approaching their patients. Clinic providers include Drs. Wasan (the study PI), Ed Heres, Cheryl Bernstein, Trent Emerick, and Susan Jarquin. If a physician is aware of a potential participant, the physician will briefly inform the participant of the research study and ask the participant for permission to be approached or called by the research team and, if permission is given, this will be documented by the physician.

Flyers will be posted in the clinic waiting rooms and exam rooms with instructions to call, email or text the study coordinators to indicate interest in their study. The research team will then contact the interested volunteer to perform the initial screening.

We are also planning to use the University of Pittsburgh Pitt+Me Registry as a recruiting tool.

Efforts will be made to attain a mix of study participants, in terms of gender and racial/ethnic representation reflective of the population of the greater metropolitan Pittsburgh area. According to the 2010 census, this distribution should be: 52% female, 48% male, 66% White, 26% Black or African American, 4% Asian, 2% Hispanic or Latino, 2% Two or More Races.

We will review our patient demographic distribution quarterly and if we find that our gender or minority recruitment is lagging we will initiate targeted recruitment strategies to increase gender or minority representation. For example, if minority recruitment is lagging, we may post flyers at other UPMC Pain Medicine clinics such as Montefiore and Mercy Hospital.

**Advertisements:** [110536A PAIN & SWALLOWING STUDY POSTER final.pdf](#)

**Screening:** Use the study's Phone Screening Form. Enter data into the form during phone interview.  
File name: [Wk0.PhoneScreeningForm.docx](#)

**Post-Screening Tasks:**  Confirm eligibility with Dr. Wasan

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- Contact volunteer about eligibility status
- If eligible, schedule Clinic Visit 1

## Compensation Schedule

Full Study Participation:	1. Clinic Visit 1: \$20 2. Clinic Visit 4: \$100
Partial Study Participation:	1. Clinic Visit 1: \$20 2. If at least half of study activities are completed: \$30
Travel Reimbursement:	Up to \$25 for travel to and from Centre Commons.



## Detailed Study Schedule with Checklists

### Clinic Visit 1

- Scheduled: Week 1  
 Location: UPMC Pain Medicine Clinic at Centre Commons, Suite 400  
 Appt. Reminder:  Research staff should call to confirm 24 hrs before appointment
- Preparation Tasks:  Print/gather paper forms:  
                                    Informed Consent: [Wk1.1.ConsentForm.docx](#)  
                                    Medical History: [Wk1.2.MedicalHistoryForm.docx](#)  
 Set up Chromebook for REDCap data entry
- Visit Tasks:  PI – Obtain informed consent. Complete Medical History  
 Staff – Enrollment Information (REDCap)  
 Subject completes REDCap surveys: PROMIS-29 & Opioid Medication Satisfaction  
 Staff – Set up subject in Mosio text messaging system & WePay system.  
 Staff – Schedule Clinic Visit 2
- Tasks After Appt.:  Order Xtampza ER from pharmacy  
 Schedule appointment reminders for Clinic Visit 2 in Mosio text message system  
 Pay subject for clinic visit in WePay - \$20 for Clinic Visit 1 & reimburse for transportation/parking

### Clinic Visit 2

- Scheduled: Week 2  
 Location: UPMC Pain Medicine Clinic at Centre Commons, Suite 400  
 Appt. Reminder: Programmed into Mosio SMS schedule. Text Name: APPT\_CLIN
- Preparation Tasks:  Set up Chromebook for REDCap data entry  
 Confirm study medication shipment with pharmacy
- Visit Tasks:  Physician – Xtampza ER administration instructions  
 Subject completes REDCap surveys:  
                                   1. Modified Baylor Dysphagia Questionnaire  
                                   2. PROMIS-29  
                                   3. Pill Swallowing Difficulty Questions  
 Staff – Schedule Clinic Visits 3 & 4 (in weeks 3 & 6).  
 Staff – Reimburse subjects for transportation/parking in WePay
- Tasks After Appt.:  Schedule appointment reminders for Clinic Visits 3 & 4 in Mosio text message system

### Clinic Visit 3

- Scheduled: Week 3  
 Location: UPMC Pain Medicine Clinic at Centre Commons, Suite 400  
 Appt. Reminder: Programmed into Mosio SMS schedule. Text Name: APPT\_CLIN
- Preparation Tasks:  Set up Chromebook for REDCap data entry

*PRO17040444: Use of Xtampza ER to overcome difficulties in swallowing opioid pills*

- Visit Tasks:
- Physician – monitor side effects & dosage
  - Subject completes REDCap surveys:
    1. Modified Baylor Dysphagia Questionnaire
    2. PROMIS-29
    3. Pill Swallowing Difficulty Questions
    4. Xtampza ER Satisfaction Question
  - Staff – Reimburse subjects for transportation/parking in WePay

### Clinic Visit 4 (End of Study)

Scheduled: Week 6  
 Location: UPMC Pain Medicine Clinic at Centre Commons, Suite 400  
 Appt. Reminder: Programmed into Mosio SMS schedule. Text Name: APPT\_CLIN

Preparation Tasks:  Set up Chromebook for REDCap data entry

- Visit Tasks:
- Physician – discuss options for future medication/dosage
  - Subject completes REDCap surveys:
    1. Modified Baylor Dysphagia Questionnaire
    2. PROMIS-29
    3. Pill Swallowing Difficulty Question
    4. Xtampza ER Satisfaction Question
    5. Patient Global Impression of Change
  - Staff – Turn off Mosio text messaging for subject
  - Staff – Pay subject \$100 in WePay for study completion and reimburse for transportation/parking

Tasks After Appt.:  Download final subject data from REDCap and Mosio

### Daily Texts

Scheduled: Every day starting with Clinic Visit 1 – Weeks 1-6  
 Collection Route: Mosio text message  
 Text name: PAIN\_DIARY, MED\_DIARY

Measures Taken: Pain Diary Questions  
 Medication Diary Questions

Researcher Tasks:  Check and download Mosio study data once each week

### Weekly Surveys

Scheduled: Weeks 4 & 5  
 Collection Route: REDCap survey. Survey link sent via Mosio text message. Text name: SURVEY\_LINK

Measures Taken: Pill Swallowing Difficulty Question

PROMIS-29

Xtampza ER Satisfaction Question (Week 5 only)

Patient Global Impression of Change (Week 5 only)

Researcher Tasks:  Check and download REDCap study data once each week

## Study Measures

### Medical History

Description	Short form to collect subject's demographic information, medical and psychiatric history.
Data Entry by	Study Physician
Data Collection Route	Paper
Equipment/Supplies	<a href="#">Wk1.2.MedicalHistoryForm.docx</a>

### Medication Diary

Description	One daily question to monitor Xtampza ER use and compliance.
Data Entry by	Subjects
Data Collection Route	Mosio SMS
Data Collected	Q1: Did you remember to take your study medication yesterday? Text Y or N.

### Medication Satisfaction Questions

Description	Brief questions to determine the subject's satisfaction with their current opioid pain medication.
Data Entry by	Subjects
Data Collection Route	REDCap
Data Collected	<p>Week 1 – Opioid Medication Satisfaction Question:            How satisfied are you with your current opioid medication?            0-----10            Not satisfied at all      Completely satisfied</p> <p>Weeks 3, 5 &amp; 6 – Xtampza ER Satisfaction Question:            How satisfied are you with the study medication, Xtampza ER?            0-----10            Not satisfied at all      Completely satisfied</p>

### Modified Baylor Dysphagia Questionnaire

Description	Swallowing difficulty questionnaire used at Baylor Medical Centers (questions 1-11)
Data Entry by	Subjects
Data Collection Route	REDCap
Data Collected	<ol style="list-style-type: none"> <li>1. Complaints regarding swallowing</li> <li>2. Date of onset of swallowing problems</li> <li>3. Swallowing problems currently experienced</li> <li>4. Food intake information</li> </ol>

Original  
Documentation <https://www.baylorhealth.com/>

### Pain Diary

Description Two daily questions about the subject's pain; questions #5 and 6 from the Brief Pain Inventory.

Data Entry by Subjects

Data  
Collection Route Mosio SMS texts

Data Collected Q1: What is your level of pain now? Text 0-10. 0 = no pain, 10 = pain as bad as you can imagine.  
Q2: What was your average level of pain over the last 24 hours? Text 0-10. 0 = no pain, 10 = pain as bad as you can imagine.

### Pill Swallowing Difficulty Questions

Description Brief question to determine current level of swallowing difficulty

Data Entry by Subjects

Data  
Collection Route REDCap

Data Collected Week 1: Do you have difficulty swallowing medications?  
If yes, how would you rate the difficulty swallowing your current opioid pain medications?  
0-----10  
No trouble at all      The greatest difficulty possible

Weeks 2-6: How would you rate the difficulty swallowing this study pain medication?  
0-----10  
No trouble at all      The greatest difficulty possible

### PROMIS-29 Adult Profile v2.0 (Participant Version)

Description Adult Profile 29-item instrument that contains a fixed collection of short forms measuring several physical and emotional domains.

Data Entry by Subjects

Data  
Collection Route REDCap

Data Collected Physical Function Score = sum of q1 - q4 (range 4-20)  
Anxiety Score = sum of q5 - q8 (range 4-20)  
Depression Score = sum of q9 - q12 (range 4-20)  
Fatigue Score = sum of q13 - q16 (range 4-20)  
Sleep Disturbance Score = sum of q17 - q20 (range 4-20)  
Social Roles Score = sum of q21 - q24 (range 4-20)  
Pain Interference Score = sum of q25 - q28 (range 4-20)  
Pain Intensity Score = answer to q29 (range 0-10)  
See PROMIS Profile Scoring Manual for more information.

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Original Documentation	<a href="https://www.assessmentcenter.net">https://www.assessmentcenter.net</a>
References	Cella, D., et al. (2010). "The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005-2008." <i>J Clin Epidemiol</i> <b>63</b> (11): 1179-1194.

### Text Message Compliance

Description	Record of whether and when subjects answered text message questions.
Data	
Collection Route	Mosio SMS
Data Collected	Answer received (y/n), time of receipt

### Urine Pregnancy Test

Description	“Dipstick” test for pregnancy in female subjects of child-bearing age
Data	
Collection Route	Urine Pregnancy Tests
How to Administer	Administer during the collection for the urine toxicology test listed above. Place dipstick in specimen cup and check for results before sealing cup for shipment pick-up.

### Weekly Survey

Description	Weekly survey; includes pain, psychological evaluations & swallowing difficulty
Data Entry by	Subjects
Data	
Collection Route	REDCap (link send via Mosio SMS)
Data Collected	Pill Swallowing Difficulty Question PROMIS-29 – full survey

## Text Message Scripts

### **TEST**

Text Contents	<Welcome to the research study! Did you receive this message? Text Y or N>
Allowed Answer Types	Yes or No
Branching	If Y, text <Thank you!>
Compliance Data	Time sent, Time received, Did subject respond

### **APPT\_CLIN**

Text Contents	<You have a research appointment at UPMC Pain Medicine at Centre Commons tomorrow, [DATE], at [TIME]. Text Y to confirm or N to cancel.>
Allowed Answer Types	Yes or No
Branching	If Y, text <Thank you. See you tomorrow!> If N, text <OK. A researcher will be in touch shortly to re-schedule your appointment.>
Notes	Mosio will notify research coordinator of subject cancellation

### **PAIN\_DIARY**

#### *Question 1*

Text Contents	<What is your level of pain now? Text 0-10. 0 = no pain, 10 = pain as bad as you can imagine.>
Allowed Answer Types	Numeric: 0-10 scale
Compliance Data	Time sent, Time responded, Did subject respond

#### *Question 2*

Text Contents	<What was your average level of pain over the last 24 hours? Text 0-10. 0 = no pain, 10 = pain as bad as you can imagine.>
Allowed Answer Types	Numeric: 0-10 scale
Compliance Data	Time sent, Time responded, Did subject respond

### **MED\_DIARY**

Text Contents	<Did you remember to take your study medication yesterday? Text Y or N.>
Allowed Answer Types	Yes or No
Branching	If Y, text <Thank you.> If N, text <Remember to take all of your prescribed medication. This is an important part of your treatment.>
Compliance Data	Time sent, Time responded, Did subject respond

# Statistical Analysis Plan

## Outcomes to be Analyzed

### Primary Outcome

#### Pain Intensity

- Weekly average pain: PROMIS-29 Pain Intensity
- Daily average pain: Text Message Pain Diary Questions

### Secondary Outcomes

#### Swallowing Satisfaction

- Pill Swallowing Difficulty Questions

#### Pain Interference

- PROMIS-29 Pain Interference

#### Medication Satisfaction

- Opioid Medication Satisfaction Question
- Xtampza ER Satisfaction Question

#### Swallowing Difficulty

- Modified Baylor Dysphagia Questionnaire

#### Mental Health Outcomes

- PROMIS-29 Depression
- PROMIS-29 Anxiety
- PROMIS-29 Satisfaction with Social Roles
- PROMIS-29 Sleep Disturbance
- PROMIS-29 Fatigue

#### Physical Health Outcomes

- PROMIS-29 Physical Function

#### Impression of Change

- Patient Global Impression of Change



## Overview of Analysis Plan

The primary outcome of changes in pain is calculated by comparing average pain level at baseline to the average of the last four weeks of treatment (i.e., after the two week conversion period). This is a comparison of the average of the seven days of average pain ratings between weeks 1 and 2 to the average of the weekly average pain intensity ratings collected on the PROMIS-29 questionnaires (pre vs. post). The comparisons of pre vs post will be done with an analysis of covariance (ANCOVA), which permits inclusion of relevant covariates, such as the baseline level of pain. The primary hypothesis is that there will be a non-inferior difference between pre-and post-pain ratings. In other words, after being converted to Xtampza ER, there will be no reported meaningful differences in the degree of pain.

The main secondary outcome is change in swallowing difficulty of opioid medication. The Pre vs Post comparisons are calculated in a similar fashion to the primary pain outcome, and compared using ANCOVA. This is a comparison between the baseline ratings of swallowing difficulties versus the average of these ratings in the last four weeks of study. The secondary hypothesis is that there will be a significant improvement in ratings of swallowing difficulties in comparing pre- vs. post scores.

The same statistical approach is taken for the other secondary outcomes, such as global impression of change, satisfaction with pain care, and side effects. We anticipate that subjects will report on average greater satisfaction with pain care, 'improved' or 'much improved' global impression of change, and comparable side effects. For any outcome, in the event of greater than 20% missing data, we will first determine if this data is missing at random. If it does appear that this is the case then we will analyze that outcome with mixed linear modeling, which produces more reliable estimates of effect sizes with such missing data.

## Study Medication

### Instructions for Prescribing Xtampza ER (from Collegium & Avella)

- Avella will provide your site with pre-paid UPS envelopes.
- Your site will place the patient enrollment form ([Wk1.3.PharmacyEnrollmentForm.docx](#)) in the pre-paid envelope and send it to Avella.
- The PI will prescribe the study drug via EPIC using Avella Orlando as the pharmacy.
- Avella will contact the PI to confirm the prescription dosage and instructions prior to dispensing
- **Please inform your subjects that they will receive a telephone call from Avella to complete a 5-minute consultation prior to dispensing the study drug.** This consultation is important to ensure that the subject takes the medication as prescribed and that Avella will address any questions that the subject may have. **This consultation is required for all subjects.**
- After Avella confirms the prescription with the PI and completes a 5-minute consultation with the subject, then Avella will dispense the study drug to the subject.
- Avella also requested that we remind your site that they are located on the East coast, which is Eastern Standard Time (EST).