Investigational Product Instruction Manual

Amgen Protocol Number (AMG 102): 20070622

Protocol Title:
Phase 3, Multicenter, Randomized, Double-Blind, Placebo Controlled Study of Rilotumumab (AMG 102) with Epirubicin, Cisplatin, and Capecitabine (ECX) as First-line Therapy in Advanced MET-Positive Gastric or Gastroesophageal Junction Adenocarcinoma

Protocol Date: 12 June 2012

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1.0 Study Contacts

Please contact your designated Clinical Monitor if you have any questions about the study, investigational product (IP) or this instruction manual.

Primary Contact

*Clinical Monitor:*

*Please Place Business Card / Contact Information here*

Please contact Investigator to obtain Site Contact Form for additional study contact details.

2.0 Investigational Product and other Protocol Required Products

Investigational Product Instruction Manual (IPIM) is the central repository for all Investigational Product (IP) management documents at the investigational site and should be made available to the Clinical Monitor as required. Copies of IP management documents may also be kept in each subject’s source document file if desired.

**Note:** In several countries, IP is referred to as Investigational Medicinal Product (IMP). In this document, IMP will be referred to as IP.

Clinical Monitor visits will be recorded on the Sponsor Visit Log (Appendix 1).

2.1 Investigational Product

In accordance with the protocol the following will be referred to as IP:

- Rilotumumab (AMG 102)
- Rilotumumab-placebo

For each of the IP used, the preparation procedure(s) and storage condition(s) should comply with the instructions provided for each and every dose of the IP that is administered.
2.2 Description of Investigational Product

Rilotumumab is a fully human monoclonal antibody (IgG2) against human hepatocyte growth factor/scatter factor (HGF/SF) that blocks binding of HGF/SF to its receptor MET, inhibiting HGF/MET-driven activities in cells.

IP will be administered intravenously through a peripheral line or indwelling catheter using a nonpyrogenic, low protein binding filter with a 0.2- or 0.22-micron pore size in-line filter infusion set-up.

Medical devices (eg, syringes, sterile needles, alcohol prep pads, in-line filters), that are commercially available are not usually provided or reimbursed by Amgen (except, for example, if required by local regulation). The Investigator will be responsible for obtaining supplies of these devices.

Rilotumumab-placebo will be provided as a sterile protein-free solution in similar vial size and appearance to rilotumumab and stored the same as rilotumumab.

2.3 Other protocol required products.

The chemotherapy medications for this study are epirubicin (E), cisplatin (C), and capecitabine (X), commonly referred to as ECX. These medications are non-Amgen medicinal products and are considered to be Investigational Product in certain countries according to the EU regulatory/definition/requirement and will be provided as required in the applicable countries. See Section 11.0 for country details.

- Epirubicin is an anthracycline cytotoxic agent which inhibits nucleic acid (DNA & RNA) and protein synthesis and interferes with replication and transcription of DNA.
- Cisplatin is a non-cell cycle specific chemotherapeutic agent which induces DNA cross-linking. Epirubicin and cisplatin will be administered intravenously.
- Capecitabine is an oral fluoropyrimidine (chemotherapy agent) which interferes with RNA and DNA synthesis when it converts to 5-flourouracil (5-FU). Capecitabine will be administered twice a day, orally.

These drugs will be formulated, packaged, labeled, and stored according to local manufacturer, supplier, and institutional procedures.
2.4 Protocol required drugs that are not Amgen products

It is expected that any protocol required drug that is not an Amgen product is inspected and verified upon receipt against the relevant product specifications and for evidence of counterfeit, tampering or other suspicious activity.

If the material is suspected of counterfeit, tampering, or other suspicious nature, designate "Receiving Hold" until a proper investigation can be initiated and escalate to Clinical Monitor within 1 business day.

Minimum information should include:

- Contact information
- Product in question
- Nature of potential incident

2.5 Packaging and Formulation

Rilotumumab and rilotumumab-placebo:

Rilotumumab (AMG 102) will be presented as sterile, colorless to slightly yellow liquid in a 10 cc vial. The formulation for IP is 30 mg/mL, formulated with 9% sucrose, 10 mM sodium acetate, and 0.004% polysorbate 20 at pH 5.4. Each vial of IP will contain approximately 8 mL of study medication. Vials are appropriately overfilled to ensure that a sufficient deliverable dose is provided, and each vial is intended for single use only.

Both 0.9% saline and 5% dextrose are acceptable for use as IV diluents.

Rilotumumab-placebo will be presented in identical containers as the IP. The formulation for placebo is 9% sucrose, 10 mM sodium acetate, and 0.004% polysorbate 20. The presentation, is 8 mL fill of sterile, colorless to slightly yellow liquid in a 10 cc vial.

The package lot number (or box number) of investigational product (active drug, placebo or active control medication) is to be recorded on each subject's Drug Administration case report form. For blinded studies, this should be done in a manner such that a subject's treatment assignment will not be unblinded during the clinical study.
Rilotumumab and rilotumumab-placebo will be supplied to the sites in 6 single-use 10 cc vial packs.

2.6 Product Labels for Investigational Product

Information provided on the labels for the IP will comply with ICH, GCP and local regulatory requirements.

Example Product Label:

![Example Product Label Image]

Example Box Label:

![Example Box Label Image]
Patient Cards (where applicable)
Certificate of release (where applicable)
2.7 Receipt and Storage of Investigational Product

Upon receipt, and to ensure stability of the IP, it must be stored under the conditions specified below.

Information with regard to temperature recording and excursions can be found in section 4.

Rilotumumab and rilotumumab-placebo

Rilotumumab / rilotumumab-placebo will be provided in liquid form in 10 cc single-use glass vials.

Rilotumumab (AMG 102) is shipped by air courier in a controlled temperature container that is suitable for shipping refrigerated products. IP vials will arrive in secondary box packaging and should be immediately placed in a refrigerator maintained at a set point between 2°C to 8°C in a secured location until planned use. The set point is a single temperature for the refrigerator and should remain constant as shown in the table below.

<table>
<thead>
<tr>
<th>Refrigerator Set Point (°C)</th>
<th>Acceptable Variation:</th>
<th>Acceptable Range:</th>
</tr>
</thead>
<tbody>
<tr>
<td>5°C</td>
<td>(± 3°C)</td>
<td>2°C to 8°C</td>
</tr>
</tbody>
</table>

Rilotumumab should be stored protected from light in a secure refrigerator prior to use. The IP is stable if maintained in accordance with the guidelines described above and administered within the provided expiration date.

Records of the actual storage conditions during the period of the study must be maintained (eg, records of the date and time and initials of person checking, and the "working day" temperatures of the refrigerator used for storage of study supplies, continuous temperature recordings, or regularly maintained temperature alarm systems used in conjunction with temperature recording).

Amgen must be notified if any IP undergoes temperature excursions (any temperatures outside 2°C to 8°C), or if vials become cracked or broken. IP supply exposed to temperature excursions or in cracked vials should not be administered to a subject unless Amgen personnel have advised in writing that it is acceptable to do so. The clinical IP
supply may need to be returned for destruction and replaced with a new IP shipment. The placebo should be handled identically to the IP.

**Do not:**
- Shake the IP containing vials vigorously
- Deviate from the storage temperatures above
- Directly expose the IP to CO₂ or dry ice

Failure to follow the instruction above may lead to denaturation and inactivation of the IP.

If foreign particulate matter or discoloration is observed, then contact your Clinical Monitor for further instructions.

**2.8 Transfer and/or Transportation of Investigational Product** Transfer between sites is not permitted. If your site has the need to transfer IP between the primary site and one of its satellite sites, the transfer must be authorized by Amgen. Please contact your Clinical Monitor before the transfer takes place and be aware that this may not be approved and that an alternative method of supply may be provided.

Rilotumumab may be transported under controlled conditions post dilution into intravenous (IV) bags, from a primary distribution facility or pharmacy to a secondary clinical "satellite" site for dosing.

Site must provide IP Transportation SOP for review/approval by Amgen. A copy of the SOP (if allowed by site) and the approval should be kept in the IPIM. Amgen will take into consideration:

- Distance between primary and satellite site
- Method of transportation and time to complete transportation (courier, private automobile)
- Method of packaging and how temperature is maintained
- Site documents recording transportation start/stop times, confirmation of temperatures

Transportation of prepared IP may occur provided that:
• Amgen has provided approval for prepared IP transportation

• Prepared IP will only be transported by a motorized vehicle and not by air

• Transportation will be under controlled conditions and will not be for a distance of more than 40 miles (64km) and the transport duration does not exceed 60 minutes

• If the prepared IP is maintained at 20°C to 25°C to destination, the prepared IP must be dosed within 8 hours of dilution and not to exceed a total of 8 hours from removal of the vial from the refrigerator (prior to preparation).

Amgen must be notified if the transportation of IP exceeds the guidance for temperature, distance or travel time. IP supply should not be utilized unless Amgen has advised that it is acceptable to do so. The clinical IP supply may need to be returned for destruction and replaced with a new IP shipment.

IP is to be packed for transportation to satellite site per institutional SOPs.

• If cold/gel packs or ice is used during transportation, ensure there is no direct contact between the prepared IP bag and the cold/gel packs or ice

• The contents should be protected from light at all times

2.9 Dose Calculation and Preparation Process

In order to ensure the safety of the clinical study subject it is extremely important that the correct IP is stored, dispensed, prepared, administered, and/or destroyed in accordance with the instructions provided. Worksheets are provided to facilitate this process.

Before preparation check that IP:

• is not expired

• has not been subjected to an undispositioned potential temperature excursion

• There are no visible particles of discoloration

Completion of a Countersignature Form (see Appendix 5) is required for Amgen Product in vials unless Amgen has approved the use of an equivalent.
The Amgen Investigational Product Countersignature Form (Form 033096) will be used during the preparation process to document that the correct dose has been prepared in accordance with the IVRS or IWRS confirmation. This form will be completed by the "Preparer" and verified by a separate person "the Verifier".

A process has been established within Amgen for requesting exemptions for the Countersignature Process. Please contact your Clinical Monitor in order to discuss if an exemption can be allowed.

**The IP Preparer must be:**

A Qualified Health Care Professional such as: Clinical Trial Pharmacist, Pharmacy Technician, Site Pharmacist, Study Nurse, Study Coordinator (as training and local requirements allow), Principal Investigator or Sub-Investigators. The Preparer must be qualified by training to prepare medicinal products.

**The Verifier must be:**

A Qualified Health Care Professional such as: Clinical Trial Pharmacist, Site Pharmacist, Study Nurse, Study Coordinator (as training and local requirements allow), Principal Investigator or Sub-Investigators.

**Reminder:** Amgen prefers that every staff member involved in the preparation of IP or completion of forms should be listed on the Delegation of Authority (DoA) log. Amgen requires that at least 1 of the 2 individuals signing on the Counter Signature form must be listed on the DoA log. If the Verifier is not listed on the DoA log then the Preparer must be on the DoA as one of the 2 signatories.

Completion of an "Exception" form is required if neither a member of the study staff listed on the DoA log nor a qualified healthcare professional is available to verify the IP preparation, to allow a non-DoA listed ("Other") individual to fulfil this role. Please contact your Clinical Monitor in order to discuss if an exemption can be allowed.

Completed counter signature forms should be filed in Appendix 5 of this IPIM.
2.9.1 Dose Calculation

Dose will be calculated through the Electronic Trial Operations (ETO) system (Interactive Voice Response System/Interactive Web Response System [IVRS/IWRS]) but the pharmacist/designee at the investigator's site must review the calculation to ensure that it is appropriate and to ensure that the calculation is based upon accurate data. A dose calculation worksheet (see Appendix 2) is provided to assist this review. Any discrepancy must be reported to Amgen.

Subject Evaluation:

1. Obtain subject's weight prior to calling IVR or dose calculation
2. Obtain the subject pre-infusion vital signs and blood work.
3. Notify the investigator if subject is unable to receive the infusion.

Dose Calculations:

1. If using an ETO system, the IVRS or IWRS confirmation will provide instructions on which vials to remove from the refrigerator and the total dose to administer to the subject.

2. As the study is blinded, dose (mg) cannot be known, however, the volume (mL) can be verified since all subjects will receive the volume expected for a dose of AMG 102 15 mg/kg, per protocol.

3. Calculate the amount (mL) of the IP needed based upon the subject's actual body weight (see example IP dose calculation worksheet).

Subject weight (kg) x dose required per protocol (mg/kg) / 30 mg/mL = Total mL of IP to be diluted with 5% dextrose or 0.9% saline for IP administration

eg, [(70 kg) x (15mg/kg)] = (1050 mg)/ 30mg/mL
= 35 mL total volume of IP to be diluted with 5% dextrose or 0.9% saline for IP administration
4. Remove appropriate number of vials from refrigerator. Vials should be inspected visually for particulate matter and discoloration. **If foreign particulate matter or discoloration is observed, do not administer.**

The final concentration of AMG 102 in the IV bag after dilution must be between 0.7 to 14 mg/mL regardless of bag size used.

Use of 100mL IV bags containing 5% dextrose or 0.9% saline is preferred when preparing AMG 102 infusion.

For this blinded study, the dose in mg cannot be confirmed or prescribed. All doses will be in mL and MUST be administered per the IVRS dosing confirmation.

To confirm your subject has been assigned the correct dose by IVRS/IWRS, see the following:

- The dose of IP will be calculated based on the subject's actual body weight at screening or the visit that is closest to the date of randomization (baseline, pre-dose)
- IVRS/IWRS will accept the weight in kg to the nearest one decimal place
- If the subject's weight changes by ≥ 10% from the initial or previously collected weight, the calculated dose from the volume of IP must be recalculated with the new weight, by entering updated weight information into the IVRS/IWRS

2.9.2 Drug Preparation Instructions (may include IP and other protocol required drugs)

Rilotumumab and rilotumumab-placebo must be stored at 2°C to 8°C through the expiration date. Upon removal from the refrigerator the vial may be kept at 20°C to 25°C (room temperature), protected from light. However the total time between removal of IP from the refrigerator through to the end IV administration must not exceed 16 hours at room temperature (8 hours for storage time in the vial at room temperature and 8 hours from time of dilution of the IP to the end of the IP infusion at room temperature, refer to Table 2). The maximum storage time of the diluted IP in the IV bag, from start of dilution to end if IP infusion, must not exceed 8 hours. Any opened IP vial not used for study administration within this time duration must be discarded. After removal from the refrigerated condition,
vials should be gently swirled to ensure mixing. **Do not shake or freeze IP.** Mixing may result in the formation of small bubbles, which is normal.

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Maximum storage time of unopened vial</th>
<th>Maximum storage time of diluted IP in IV bag (from start of dilution to end of IP infusion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20°C to 25°C 68°F to 77°F (room temperature)</td>
<td>8 hours</td>
<td>8 hours</td>
</tr>
<tr>
<td>2°C to 8°C 36°F to 46°F (refrigerated)</td>
<td>Per expiration date provided by Amgen</td>
<td>24 hours</td>
</tr>
</tbody>
</table>

**Dilution of IP for IV Administration:**

Preparation of the clinical supplies should be performed using aseptic techniques and under sterile conditions. Prolonged exposure to light should be avoided. Use 5% dextrose or 0.9% saline as diluent.

When preparing the IP, the final concentration should be between 0.7 mg/mL to 14 mg/mL in 5% dextrose or 0.9% saline. See guidelines are as follows:

<table>
<thead>
<tr>
<th>Subjects assigned total dose volume of IP</th>
<th>Volume of IV bag for admixture</th>
</tr>
</thead>
<tbody>
<tr>
<td>up to 23 mL</td>
<td>50 mL</td>
</tr>
<tr>
<td>2.4 mL to 46 mL</td>
<td>100 mL</td>
</tr>
<tr>
<td>3.5 to 69 mL</td>
<td>150 mL</td>
</tr>
<tr>
<td>5.9 to 116 mL</td>
<td>250 mL</td>
</tr>
</tbody>
</table>

If larger sized IV bags are not available, the IP dose volume to be administered should be distributed equally between two or more 100 mL IV bags as required.
Alternatively the volume of diluent removed from the IV bag prior to injecting the IP can be reduced provided that the final concentration of IP remains between 0.7mg/mL and 14 mg/mL.

1. Clean the port of the IV bag of 5% dextrose or 0.9% saline, with an alcohol wipe.

2. Remove a volume of 5% dextrose or 0.9% saline from the IV bag equivalent to the total volume of IP to be injected and discard.

3. Remove cap from the IP vials and clean rubber stopper with alcohol wipe.

4. Slowly withdraw the required amount of the IP solution from the vial(s) and inject the IP solution into the infusion bag. When injecting the IP into the infusion bag, direct the stream to the side of the bag to minimize the agitation of the solution.

5. Gently invert the infusion bag to mix. Do not shake. Do not transport the infusion bag using mechanical transport systems such as pneumatic-tube systems that may cause vigorous agitation of the solution. Inspect for particulate matter and discoloration. Do not administer if particulate matter or discoloration is observed.

6. After preparation, the intravenous solution must be used at controlled room temperature of 20°C to 25°C (68°F to 77°F) within 8 hours of IP dilution. If the intravenous solution cannot be administered immediately (within the hour of mixing), the solution may be kept in refrigerated temperature, 2°C to 8°C (36°F to 46°F), but must be brought back to room temperature prior to administration and used within 24 hours of preparation.

Protect from light and DO NOT FREEZE.

All prepared IV bag must be labeled prior to administration according to local institutional guidelines. Amgen recommends the following information:

- Study number
- Subject identification number
- Subject initials (if permitted by local practices)
- Date and time of preparation and expiration
- Initials of preparer
Insert completed IP or other protocol required drug preparation worksheet(s) into Appendix 2 and Appendix 3, as applicable.

2.10 Dispensing and Administration of Prepared IP or Other Protocol Required Drug

Upon completion of preparation consider the following:

- In order to ensure the safety of the clinical study subject it is extremely important that the correct IP is stored, dispensed, administered and/or destroyed in accordance with the instructions provided.

- IP must be properly labeled and dispensed in accordance with current ICH GCP and local/regional requirements prior to dispensing for administration.

- Only individuals listed on the Delegation of Authority Form (DoA) as authorized to dispense, prepare and administer IP may do these activities.

- The Clinical Monitor will review source documentation as well as other site documentation to confirm only authorized staff are involved in the prescribing, preparation and administration processes.

- Adequate source documentation (in addition to IP accountability logs) per GCP and ICH guidelines regarding IP administration must be maintained by the clinical site staff for review and inspection by the Clinical Monitor at each visit. This may include medical records, prescriptions, medication orders, medication flow sheets, dose calculation and preparation worksheet(s) etc.

Materials Inventory

The recommended infusion supplies are given below:

- Primary Infusion Set (PVC-DEHP, PVC non-DEHP, non-PVC non-DEHP, or non-PVC non-DEHP polybutadiene sets, blunt needle system), interlink Y-site

- Secondary Infusion Set (PVC-DEHP, PVC non-DEHP, non-PVC non-DEHP, or non-PVC non-DEHP polybutadiene sets, blunt needle system)

- Heparin Locks: BD Q-Syte connector with 6" DEHP tubing (optional)

- BD 22 GA, 1.00 IN peripheral catheter
- IV bag 5% dextrose or 0.9% saline, 50 mL, 100 mL, 150 mL or 250 mL volume, depending on volume of IP to be added (PVC or partial additive [polyethylene/polyolefin mixture] bag)
- low protein binding filter with a 0.2- or 0.22-micron pore size

Administration of IP:

1. Select IV infusion site, IP may be infused peripherally or through a central venous catheter. Follow the policies of your institution for IV insertion and medication infusion.

2. The IP should not be infused concomitantly in the same IV line with other medications.

3. Set the infusion rate to properly deliver IP solution per below: (eg. IV pump or via gravity drip). Do not administer as IV push or bolus.
   - On the first day of administration (eg. Cycle 1 Day 1), the final solution should be administered over 60 minutes.
   - If well tolerated, IP solution can be infused over 30 minutes in subsequent cycles.
   - Infusion times can be extended to a maximum of 120 minutes for subjects unable to tolerate the 60 minute infusion especially for volumes greater than 100 mL.

Important: If a hypersensitivity reaction occurs, stop the infusion and immediately contact the attending physician (investigator or sub-investigator).

Refer to protocol Section 6.1.3.1.1 for management guidelines for IP infusion reactions.

4. Once infusion is complete, flush or push with 5% dextrose or 0.9% saline to infuse any residual IP remaining in the tubing.

Do not use any non recommended solutions (eg, Albumin) for flushing either before or after administration of medication.

Discard the catheter and tubing according to local requirements.
The Rilotumumab is to be administered prior to the ECX chemotherapy.

**Administration of Non-Amgen Investigational Products:**

**ECX Chemotherapy**

Each cycle of ECX will consist of the following: epirubicin 50 mg/m² day 1 IV, cisplatin 60 mg/m² day 1 IV, and capecitabine 625 mg/m² BID orally days 1-21 given every 3 weeks.

A maximum of ten cycles of ECX will be administered to subjects.

The Body Surface Area (BSA) does not need to be recalculated unless there is a change in weight of more than 10% compared to baseline. For subjects with extreme BSA (e.g. ≥ 2.3), investigators should contact Amgen with questions regarding dose modification.

Prior to chemotherapy administration, the investigator or designee must review hematology, chemistry, creatinine clearance, liver function tests, and the presence of hematologic and non-hematologic toxicities no more than 3 days prior to dosing (within 7 days prior to Cycle 1 day 1) to determine treatment suitability.

**ECX Antiemetics and Hydration**

Antiemetics should be routinely administered to all subjects prior to chemotherapy administration on Day 1 according to institutional practice. Oral antiemetics should also be provided post-chemotherapy according to local guidelines.

Pre- and post-cisplatin hydration and electrolyte replacement should be administered according to institutional practice.

A suggested schedule for hydration is as follows:

1. Prehydration - 1000 mL of normal saline IV over 2 to 4 hours prior to cisplatin
2. Mannitol 12.5 gm IV bolus immediately prior to or admixed with cisplatin
3. Posthydration: 1000 to 1500 mL normal saline over 2 to 4 hours following cisplatin administration
4. Potassium chloride and/or magnesium sulfate should be added to the hydration
solutions per institutional practice.

**Epirubicin Administration (E)**

- Epirubicin 50 mg/m2 will be administered as an IV bolus over 10 ± 2 minutes
- For storage, preparation and administration information, please refer to the most current prescribing information in your region.

**Cisplatin Administration (C)**

- Cisplatin 60 mg/m2 will be administered in normal saline over 1-4 hours (± 15 minutes) according to local standard institutional practice following the Epirubicin bolus.
- For sites participating in IPK assessments, on days that cisplatin PK samples are drawn, cisplatin must be administered over 2 hours.
- For storage, preparation and administration information, please refer to the most current prescribing information in your region.

**Capecitabine Administration (X)**

- Capecitabine tablets are available in 500 mg and 150 mg and should be administered morning and evening and swallowed with water. Missed doses of capecitabine should not be made up. For sites participating in IPK assessments, on days that capecitabine PK samples are drawn, subjects will be asked not to take the morning dose of capecitabine at home.
- The dosage of capecitabine should be rounded to the nearest dose that permits administration of only whole tablets of capecitabine. Subjects should not be prescribed a dose that requires splitting of capecitabine tablets. In addition, subjects should be instructed not to dissolve, crush or chew capecitabine tablets. Investigators should refer to Table 4.1 for dosing instructions for capecitabine. Once an exact dose has been calculated, the corresponding rounded dose should be taken twice daily.
For storage, preparation and administration information, please refer to the most current prescribing information in your region.

Table 4.1 Dosage of Capecitabine (625mg/m² BID):

<table>
<thead>
<tr>
<th>Exact Dose (mg)</th>
<th>Rounded Dose (mg)</th>
<th>500mg</th>
<th>150mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>450 - 575</td>
<td>500</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>576 - 725</td>
<td>650</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>726 - 900</td>
<td>800</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>901 - 975</td>
<td>950</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>976 - 1075</td>
<td>1000</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>1076 - 1225</td>
<td>1150</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>1226 - 1375</td>
<td>1300</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>1376 - 1475</td>
<td>1450</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>1476 - 1575</td>
<td>1500</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>1576 - 1725</td>
<td>1650</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>1726 - 1875</td>
<td>1800</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>1876 - 1975</td>
<td>1950</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>1976 - 2075</td>
<td>2000</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>2076 - 2225</td>
<td>2150</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

2.11 Dispensing and instructions for take home medications

Capecitabine should be dispensed to the subjects along with the Capecitabine Daily Subject Drug Diary, for self administration (swallowed with water), morning and evening. Subjects will be expected to record the dose taken and time of dosing in their Subject Drug Diary. Subjects are to be instructed to not make up a missed dose. At each visit cycle, subjects will be expected to bring their diary and remaining capecitabine tablets with them for accountability. A new Capecitabine Daily Subject Drug Diary is to be dispensed to subject on Day 1 of each visit cycle.

For sites participating in IPK assessments, on days that capecitabine PK samples are drawn, subjects will be asked to not take the morning dose of capecitabine at home. An
example of the Capecitabine Daily Subject Drug Diary to be provided to subjects is located at Appendix 18.

2.12 Access to Treatment Assignments

Note: When appropriate Amgen will provide an unblinded Clinical Monitor.

The investigator should ensure that access to the relevant IVRS/IWRS account is verified and active and that it is possible to access blinded information if required. Additional information about the access levels is contained within the IVRS/IWRS manual in Appendix 14.

In blinded studies IP will be assigned to specific subject numbers who will receive specific individual boxes of IP which will be provided using IVRS/IWRS.

Authorised staff will be provided with a unique Personal ID number (PIN) to access the IVRS/IWRS. PINs will be assigned to site staff with an applicable level of access which could include access to the unblinding module in the ETO/IVRS to obtain unblinding information. The PIN is unique to the individual site staff member to whom it has been provided and must not be shared. Should a new PIN be required contact the Clinical Monitor.

A subject’s treatment assignment should only be unblinded when knowledge of the treatment is essential for the further management of the subject.

The investigator is strongly encouraged to contact the Amgen Clinical Study Manager before unblinding any subject’s treatment assignment, but must do so within 1 working day after the event and must document the unblinding in the subject’s case report form and subject source document.

3.0 Product Complaints

Amgen would like you to report any concerns or irregularities about the packaging, appearance or usage of IP or other protocol required drug by contacting the Clinical Monitor. To assist consideration of the complaint please complete the Product Complaint Form (see Appendix 4) and have all required documentation available when you speak to the Clinical
Monitor. Provide a copy of the completed form to the Clinical Monitor and also file within Appendix 4.

Amgen is interested in hearing about any concern or irregularity at any stage of the study. Should any such concerns or irregularities occur, please do not use the IP or other Amgen provided protocol required drug until Amgen confirms that it is permissible to use.

The following could be considered potential product complaints that need to be reported to Amgen:

- Packaging: for example, broken container or cracked container
- Devices: issues with delivery of IP by device
- Usage: for example, subject or healthcare provider cannot appropriately use the product
- Labeling: for example, missing labels, illegible labels, incorrect labels, and/or suspect labels
- Change in IP appearance: for example color change or presence of foreign material
- Unexpected quantity in bottle: for example number of tablets or amount of fluid
- Evidence of tampering or stolen material

If possible, please have the IP or other Amgen provided protocol-required drug /suspect item available for examination when making the call for a product complaint. Maintain IP or other Amgen provided protocol-required drug /suspect item at appropriate storage conditions described in this manual until further instructions are received from Amgen. You will also be asked for the following, site location and name of institution/investigator, protocol number, product name, lot number (from label), date problem was noticed, a full description of the problem and whether or not a subject was dosed with the impacted product/device.
4.0 Investigational Product Storage and Temperature Monitoring

Refrigeration or freezer units used to store all IP should be properly maintained (in accordance with manufacturer’s instructions) and monitored. Additionally, a temperature log must be maintained for all refrigerators storing IP (including IP that is stored at room temperature) and the actual temperature and range of temperatures must be recorded each day that the site is open using an appropriate tool such as the temperature log in Appendix 6.

Different tools may be appropriate to monitor temperature. Please check with your Clinical Monitor to confirm that the temperature tool used at your site is appropriate and in accordance with local and Amgen requirements.

When using an electronic or automated device to record the temperature, please ensure these records are available and can be reviewed for inspection during monitoring visits.

Any print-outs of the temperature records should have documented review by site personnel in accordance with the site process.

4.1 Temperature Logs

Documentation of the IP and other protocol required drug storage temperature is mandatory. The Amgen IP temperature log is included in this manual for your use (Appendix 6), but your site may use its own institution-specific documentation for IP temperature monitoring, if such documentation is deemed equivalent to the Amgen temperature log by your Clinical Monitor.

If this is the case record Amgen’s agreement in a Note to File placed in Appendix 6.

File completed temperature logs in Appendix 6.

Note: IP(s) stored at room temperature is/are not exempt from the temperature monitoring requirements.

4.2 Temperature Requirements and Excursions

<table>
<thead>
<tr>
<th>Refrigerator Median Temperature</th>
<th>Acceptable variation</th>
<th>Acceptable range</th>
</tr>
</thead>
<tbody>
<tr>
<td>5°C</td>
<td>+/- 3°C</td>
<td>2°C to 8°C</td>
</tr>
</tbody>
</table>
4.3 Definition of Temperature Excursion

A temperature excursion occurs when products are exposed to temperatures outside the acceptable storage conditions as defined in the IPIM or outside routine IP preparation parameters, for any period of time greater than 15 minutes.

Brief temperature events (eg, temperature spikes), of durations less than 15 minutes, should be noted on the Temperature Log, but need not be reported to Amgen as Temperature Excursions, unless there are more than 3 such events in a 24 hour period. If there are more than 3 such events in a 24 hour period this should be reported as a possible temperature excursion.

Rounding rules apply: For example, if the storage conditions state “Store between 2°C to 8°C”, then a reading of 1.4°C would be rounded down to 1°C and 8.5°C would be rounded up to 9°C. Temperatures 1.4°C or below, and temperatures 8.5°C and above would thus be considered temperature excursions if >15 minutes. If <15 minutes it is not a temperature excursion.

Alternatively, a temperature of 1.5°C would be rounded up to 2°C and 8.4°C would be rounded down to 8°C. These would not be considered temperature excursions.

Note: ECX should be stored per the manufacturer’s label and recommendations.

Accordingly, for a requirement to “Store between 2°C to 8°C” the following would apply:

<table>
<thead>
<tr>
<th>Reading</th>
<th>Rounded up or down?</th>
<th>Rounded to</th>
<th>Is it a temperature excursion if event for &gt;15 minutes?</th>
<th>Is it a temperature excursion if event was for &lt;15 minutes and up to 3 events occurred in 24 hours?</th>
<th>Is it a temperature excursion if event was for &lt;15 minutes and there were more than 3 events in 24 hours?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.4</td>
<td>down</td>
<td>1</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4.4 Reporting of Temperature Excursions

When a temperature excursion occurs at a clinical site, the site staff must inform the Clinical Monitor of the temperature excursion and record all the details on the Temperature Excursion Submission Form provided in Appendix 7. Send a copy to the email address listed at the bottom of the form, and file the completed Temperature Excursion Submission Forms in Appendix 8.

4.5 Management of IP exposed to a suspected Temperature Excursion

Under no circumstances should any IP impacted by a temperature excursion be administered to clinical study subjects before the product is evaluated by Amgen. Pending such evaluation, any IP suspected of being exposed to a temperature excursion should be quarantined from viable IP under the mandatory appropriate storage conditions until Amgen has provided guidance. The IP suspected of being exposed to a temperature excursion should not be marked in any way unless instructed to do so by Amgen.

4.6 Disposition by Amgen

Amgen will provide written notification/instructions in the form of a Disposition Memo for each evaluated Temperature Excursion. This communication should be filed in Appendix 8 with the relevant Report Form.

If you currently have subjects on-study and receiving IP, you will need to inform your Clinical Monitor that your site will require an immediate re-supply shipment as suspect IP must not be administered to subjects until deemed acceptable by Amgen.

An example of the type of notifications you may receive from Amgen follows:
Example of notification that Amgen will send to you if you report a temperature excursion

Dear Temperature Excursion Reporter,

I would like to inform you of the assessment for a temperature excursion that occurred at site , study , while was reported on 12-June-2008.

Temperature Excursion Reported

During storage at site, the product was exposed to a temperature below 2 °C for 30 minutes (minimum temperature 0 °C)

You informed us that the below mentioned products were already administered to subjects before the temperature excursion was reported to Amgen QA.

Based on the Temperature evaluation form, internal investigation with regard to the lot history and stability data, the following disposition decision was made by the ELC QP / Amgen Quality Assurance:

Product Name

The quality of the products mentioned below was not compromised when the product was administered to subjects.

<table>
<thead>
<tr>
<th>Package Lot Number</th>
<th>Box Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>L007008</td>
<td>2 boxes</td>
</tr>
<tr>
<td>L007326</td>
<td>3 boxes</td>
</tr>
</tbody>
</table>

The quality of the following products at the time the product was administered to subjects cannot be determined as our stability program does not cover the temperature excursion as described above.

<table>
<thead>
<tr>
<th>Package Lot Number</th>
<th>Box Number</th>
</tr>
</thead>
</table>

If the quality of the products could not be determined then please contact study management to discuss how to proceed.

If you have any further questions, please do not hesitate to contact me.

Tom van Nilen  (Electronic Signature on File) / 17-Jun-2008
Quality Rep Signature/Date
5.0 Investigational Product Accountability

Amgen, as a sponsor of clinical studies, requires investigators to establish a record of receipt, storage, use and disposition of all IP listed in section 2 and other protocol required drugs listed in section 2.3, if provided to the site by Amgen. The investigator is responsible for ensuring that accountability is maintained and accurate at his/her clinical site.

Amgen uses the following documents to support/ensure IP accountability:

- Proof of Receipt
- Master Investigational Product Accountability Record
- Temperature Logs
- Temperature Excursion Submission Form
- Return of Investigational Product for Destruction
- Final Investigational Product Reconciliation Statement
- Product Extension/Expiry Memos (some countries)

5.1 Supply of Investigational Product(s) and Proof of Receipt

a) Initial supply requirements

At study initiation or as required, rilotumumab and rilotumumab-placebo will be shipped to an individual noted as responsible at the site as designated by the Investigator on the DoA Form (eg, a pharmacist) at the investigator’s institution, who will verify the contents of the shipment in accordance with the Proof of Receipt (POR) Form (manual or electronic form) and enter the required data into the POR and Master Investigational Product Accountability Record and IVRS/IWRS as applicable.

Upon receipt of product(s), access IVRS/IWRS to register receipt via Electronic POR. The original POR must be signed, dated and filed in Appendix 9 of IPIM.

b) Re-supply requirements

Resupply of IP is based on set parameters within the ETO/IVRS system. Resupply shipments will occur automatically when site supply falls below established levels within the system.
If you are in one of the countries noted below, at each subject visit that Epirubicin, Cisplatin and / or Capecitabine (ECX) is allocated to a subject, the site will be required to place an inventory adjustment call into IVRS. This will trigger re-supply shipments as needed based on the inventory level assigned to your site at activation.

<table>
<thead>
<tr>
<th>Austria</th>
<th>Belgium</th>
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<td>Romania</td>
<td>Slovakia</td>
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<tr>
<td>Ukraine</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note:** Should there be any issues with the product upon receipt, including shipping delays, refer to the instructions on the POR form. Potential temperature excursions that occur during shipping will be considered and dispositioned by Amgen. If appropriate, also refer to product complaints section (3.0)

**5.2 Master Investigational Product Accountability Record**

Accountability of IP at your clinical site is mandatory in accordance with ICH GCP. The Amgen Master Investigational Product Accountability Record template is included in Appendix 10 for your use.

Should your site wish to use its own institution specific documentation for IP accountability please discuss with your Clinical Monitor who will assess and provide feedback as to whether this will be acceptable. If appropriate record the agreement of Amgen in a Note to File and file in Appendix 10.

All Master Investigational Product Accountability Record(s), or approved equivalent will be filed in Appendix 10 of the IPIM. In the event that there is more than one formulation of a particular IP or other protocol required drug, use one Master Investigational Product Accountability Record per formulation/product.

A Master Investigational Product Accountability Record (Appendix 10) for the following IP and other protocol required drugs provided by Amgen:

- Rilotumumab (AMG 102)
- Epirubicin (E)
- Cisplatin (C)
- Capecitabine (X)

must be kept current and should contain:

- dates and quantities of rilotumumab/ECX received from Amgen
- packaged lot numbers for product(s) received
- subject's identification number as assigned by IVRS
- unique identified box or kit number if applicable add note that full box id should be used,
- date and quantity of IP dispensed (and remaining, if from individual subject drug units)
- initials of the dispenser

Please note:

- IP or other protocol-required drug accountability records, as applicable, must be maintained at each location where IP or other protocol required drug are stored (eg, main pharmacy, satellite pharmacy) and must be stored in a secure location which is only accessible to authorized personnel.
- Each protocol-required IP or other protocol required drug provided by Amgen should be accounted for on separate accountability logs.
- If site is participating in more than one Amgen sponsored study it shall have a separate accountability record must be used for each product/study.

5.3 Return or Destruction of Investigational Product

The Clinical Monitor must complete a Return of Investigational Product for Destruction (RIPD) form prior to any IP being destroyed or returned to Amgen or Amgen designee (country depot).

Epirubicin and cisplatin are cytotoxic products and should not be returned to Amgen. The site is expected to have a documented destruction process for such products and should
take all appropriate precautions and should follow the site approved destruction process. Relevant certificates of destructions should be placed in Appendix 11.

Any documentation related to the return or destruction of IP should be retained in Appendix 11.

5.3.1 Return of Investigational Product

Unless otherwise advised, at the end of the study, or as directed, all unused IP and other protocol required drug supplies that have been provided by Amgen will be returned to Amgen or Amgen designee.

If Site has a policy to destroy rather than return the unused IP and other protocol-required drug supplies, the Clinical Monitor MUST be made aware of this policy prior to any such destruction taking place. The process must be recorded on FORM-022241 (see Appendix 11).

5.3.2 Destruction of Investigational Product

For product that will not be returned to Amgen or Amgen designee (country depot) the procedure for destruction of the product should be verified by the Clinical Monitor prior to destroying any product.

5.3.3 Documentation of return/destruction

- Used and/or unused IP that is either returned or destroyed must be recorded on the Return of Investigational Product for Destruction (RIPD) Form before return. Product accountability must be conducted by the Clinical Monitor prior to return.

- The RIPD Form must be completed and included in the shipment of used and unused IP to Amgen or Amgen designee (country depot). At the end of the study, the Final Investigational Product Reconciliation Statement (FIPRS) must be completed and provided to Amgen. These forms will be completed by the Clinical Monitor who will generate a form for review and signature by the site.
• These inventories must be made available for inspection by an authorized Amgen representative or designee and regulatory agency inspectors. The investigator is responsible for all used and unused clinical study supplies.

5.4 Investigational Product Expiration and Extension Memos

Expiry information must be verified prior to IP dispensing or preparation against the product label and/or expiration memos as applicable.

If extension of the expiration date occurs, the site will receive extension labels and/or extension memos prior to the expiration date noted on product label and/or expiration memos.

Relevant documentation is filed in Appendix 13.

6.0 Devices

IP will be administered intravenously through a peripheral line or indwelling catheter using a nonpyrogenic, low protein binding filter with a 0.2- or 0.22-micron pore size in-line filter infusion set-up. These filters will not be provided by Amgen, unless required by local regulation.

The site is expected to ensure filters have not expired prior to use and to have a documented disposal process in place. Any issues identified with the filters are to be documented and reported to the applicable manufacturer.

7.0 Electronic Trial Operations system (ETO)

(Interactive Voice Recognition System/Interactive Web Recognition System [IVRS/IWRS])

Your Clinical Monitor will periodically review the IVRS/IWRS manual and instructions (see Appendix 13) to ensure that they are the most current versions available.

Please file the following documentation in Appendix 13 of the IPIM (copies of these documents may also be filed in study subjects' records and/or investigator site file):

• Fax and/or email IVRS/IWRS confirmations relating to IP
• Completed IVRS/IWRS worksheet(s)
Any other study information should be included in the subject’s study source document record.

If IVRS/IWRS allocates product that has been subject to a Temperature Excursion that has not been dispositioned contact Clinical Monitor for guidance.

8.0 Dosing Errors

If you become aware of any dosing error immediately contact your Clinical Monitor.

Examples of dosing errors are overdosing, under-dosing or incorrect dosing.

Dosages (mg/kg) will be administered based on the subject’s actual body weight during screening closest to randomization. If there is a 10% or more change in weight at the day of dosing, the dosage of IP to be administered must be recalculated. If a dose adjustment is not made, a dosing error must be reported immediately to Amgen.

A dosage overdose will also be treated as an SAE and be reported to AMGEN within 24 hours of identification of the overdose error.

9.0 Protocol / Protocol Amendments

The current version of the protocol and amendments is filed in Appendix 15.

10.0 Investigator’s Brochure

The current version of the Investigator’s Brochure is filed in Appendix 16.

11.0 Country Specific Information

The protocol required chemotherapy drugs, collectively known as ECX;

- epirubicin (E)
- cisplatin (C)
- capecitabine (X)

will be supplied according to regional regulatory guidelines in which the country is located (non-EU, EU, other regions).
11.1 Non-EU

The protocol required chemotherapy drugs (ECX), which may or may not be commercially available, are not considered IP in the following non-EU countries:

<table>
<thead>
<tr>
<th>Australia</th>
<th>Brazil</th>
<th>Canada</th>
<th>Mexico</th>
</tr>
</thead>
<tbody>
<tr>
<td>Switzerland</td>
<td>USA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The non-EU countries listed in the table above will be responsible for obtaining supplies of ECX. These drugs will not be provided by Amgen.

These drugs will be formulated, packaged, labeled, and stored according to local manufacturer, supplier, and institutional procedures. For full details and prescribing information, please see the most recent version of the labels for the drug products in the region in which they are approved.

11.1.2 European Union (EU)

The protocol required chemotherapy drugs (ECX) are considered IP in the following countries located in the EU:

<table>
<thead>
<tr>
<th>Austria</th>
<th>Belgium</th>
<th>Bulgaria</th>
<th>Czech Republic</th>
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<td>Poland</td>
<td>Portugal</td>
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<tr>
<td>Romania</td>
<td>Slovakia</td>
<td>Spain</td>
<td>Sweden</td>
</tr>
<tr>
<td>United Kingdom</td>
<td></td>
<td></td>
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</tbody>
</table>

The EU countries listed in the table above will be supplied centrally by Amgen Breda (ABR) and managed through IVRS.

These drugs will be packaged and labeled by Amgen but will be stored according to local manufacturer, supplier, and institutional procedures. For full details and prescribing information, please see the most recent version of the labels for the drug products in the region in which they are approved.

At the beginning of the study the chemotherapy drug supply will be automatically supplied to the sites based on subject enrolment. Re-supply of chemotherapy drugs will be
automatically triggered as subject visits are registered in IVRS. However, no dose delays or dose reductions are registered in IVRS, therefore, ‘inventory adjustment’ calls will need to be made to IVRS.

11.1.3 Other Regions

Ukraine
- Epirubicin and capecitabine are not considered IP and will be supplied locally by Amgen, due to import/export restrictions.
- Cisplatin is considered IP and will be supplied centrally by Amgen Breda.

Russia
- ECX are not considered IP and will be supplied locally by Amgen.

South Africa
- ECX is considered IP and will be centrally supplied by Amgen Breda.

Turkey
- ECX is considered IP and will be centrally supplied by Amgen Breda.

11.2.1 Packaging and formulation of the ECX chemotherapy

All ECX chemotherapy to be used in the countries listed in the table below will be purchased by Amgen as commercially available material in and will be covered by a full and current Marketing Authorisation issued by the respective country's regulatory authority.

<table>
<thead>
<tr>
<th>Austria</th>
<th>Belgium</th>
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<tbody>
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<td>Poland</td>
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<td>Romania</td>
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<td>Slovakia</td>
<td>South Africa</td>
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<tr>
<td>Spain</td>
<td>Sweden</td>
<td>Turkey</td>
<td>Ukraine</td>
</tr>
<tr>
<td>United Kingdom</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

11.2.2 ECX chemotherapy labelling

The product will be labeled for investigational use in accordance with Annex 13 of Directive 2001/20/EC at one of the following manufacturing sites:

Catalent UK Packaging Ltd
Lancaster Way
Wingates Industrial Park
Westhoughton
Greater Manchester
BL5 3XX
United Kingdom

Amgen Breda
Minervum 7061
4817 ZK Breda
The Netherlands

The labeling will be performed under current GMP and GCP.

Products labeled at either site will be released for investigational use in the European Union from Amgen ELC by a Qualified Person.
Product Label (where applicable)
12.0 Miscellaneous
13.0 Revisions

Date of Revision to IPIM:

<table>
<thead>
<tr>
<th>Section</th>
<th>Description / Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
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<tr>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix 1 – Sponsor Visit Log

The Sponsor Visit Log will be completed by the Clinical Monitor to record visits made.
Appendix 2 – Dose Calculation Worksheet

Completed dose calculation worksheet(s) including dose calculation confirmation(s) from the IVRS/IWRS, as applicable, should be placed here for review by the Clinical Monitor during each visit that covers situations where IP has been dispensed.
Appendix 3 – Dose Preparation Worksheet

Completed dose preparation worksheet(s) should be placed here for review by the Clinical Monitor during each visit that covers situations where IP has been dispensed.
Appendix 4 – Product Complaint Form

Please use this form to report product complaints. Contact the Clinical Monitor for assistance.

Completed forms and related correspondence should also be stored in this Appendix.
Appendix 5 – Countersignature Form

IP is provided in vials for this study and this form should be completed for each dose.
Appendix 6 – IP Temperature Log

All completed manual Investigational Product Temperature Logs will be filed in this Appendix.
Appendix 7 – IP Temperature Excursion Submission Form

Complete this form for any Temperature Excursions. Contact Clinical Monitor for assistance.
Appendix 8 – IP Temperature Excursion Forms (completed) & disposition memos

All Completed Temperature Excursion Forms and related disposition memos (including those relating to shipping) will be filed in this Appendix.
Appendix 9– Proof of receipt

All proofs of receipt will be filed in this Appendix.
Appendix 10 – Master IP Accountability Form and subject accountability record

This form should be used to record master IP accountability. Completed forms will be filed in this Appendix.
Appendix 11–Return/Destruction of IP Forms & Certificates of Destruction

The RIPD Form will be completed by the Clinical Monitor who will generate the form for review and signature by the site. A copy of the completed form should be filed in this Appendix.

If site has a policy to destroy rather than return the Clinical Monitor MUST be made aware of this policy prior to any such destruction taking place. The process must be recorded on FORM-022241 and filed here.
Appendix 12 – Final IP Reconciliation Statement

This form will be completed by the Clinical Monitor who will generate the form for review and signature by the site. A copy of the completed form must be filed in this Appendix.
Appendix 13- Expiry and Extension Memos/Documentation

File all documentation in relation to expiry and extension of IP in this Appendix.
Appendix 14 – ETO (IVRS/IWRS) Manual
Appendix 15 – Protocol/Protocol Amendments
Appendix 16 – Investigator’s Brochure
Appendix 17 – Miscellaneous

This section may be used to file other relevant documentation.
Appendix 18 – Subject Instructions

Insert Capecitabine Daily Subject Drug Diary