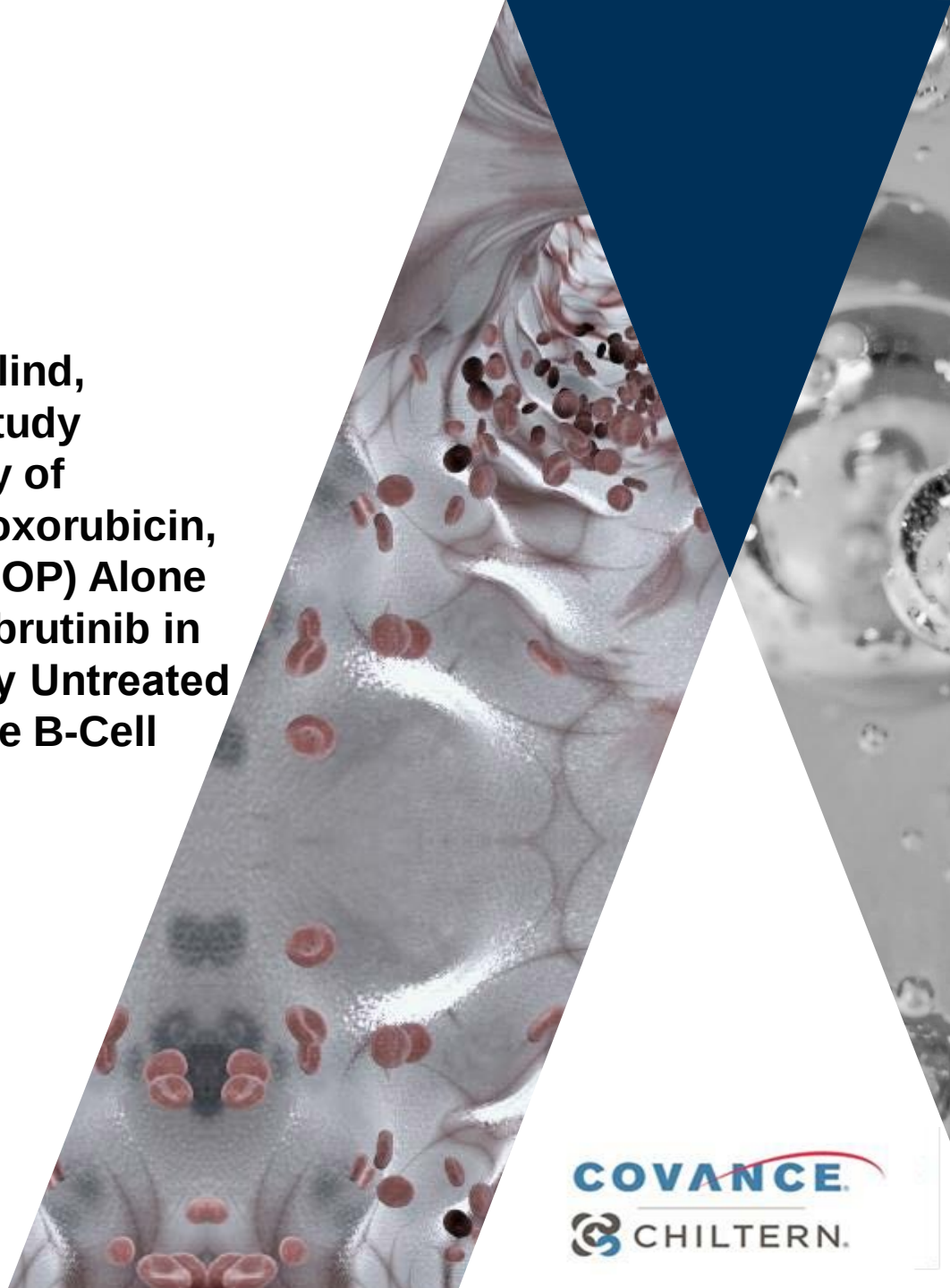
A Phase 3, Randomized, Double-blind, Placebo-Controlled, Multicenter Study Comparing the Efficacy and Safety of Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (R-CHOP) Alone Versus in Combination with Acalabrutinib in Subjects ≤65 Years with Previously Untreated Non-Germinal Center Diffuse Large B-Cell Lymphoma

Pre-Study Visit

Version 1.0_January 2020



Confidential

Agenda

- Welcome and Introductions
- Study Timelines
- Study Drug Overview
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- Study Design
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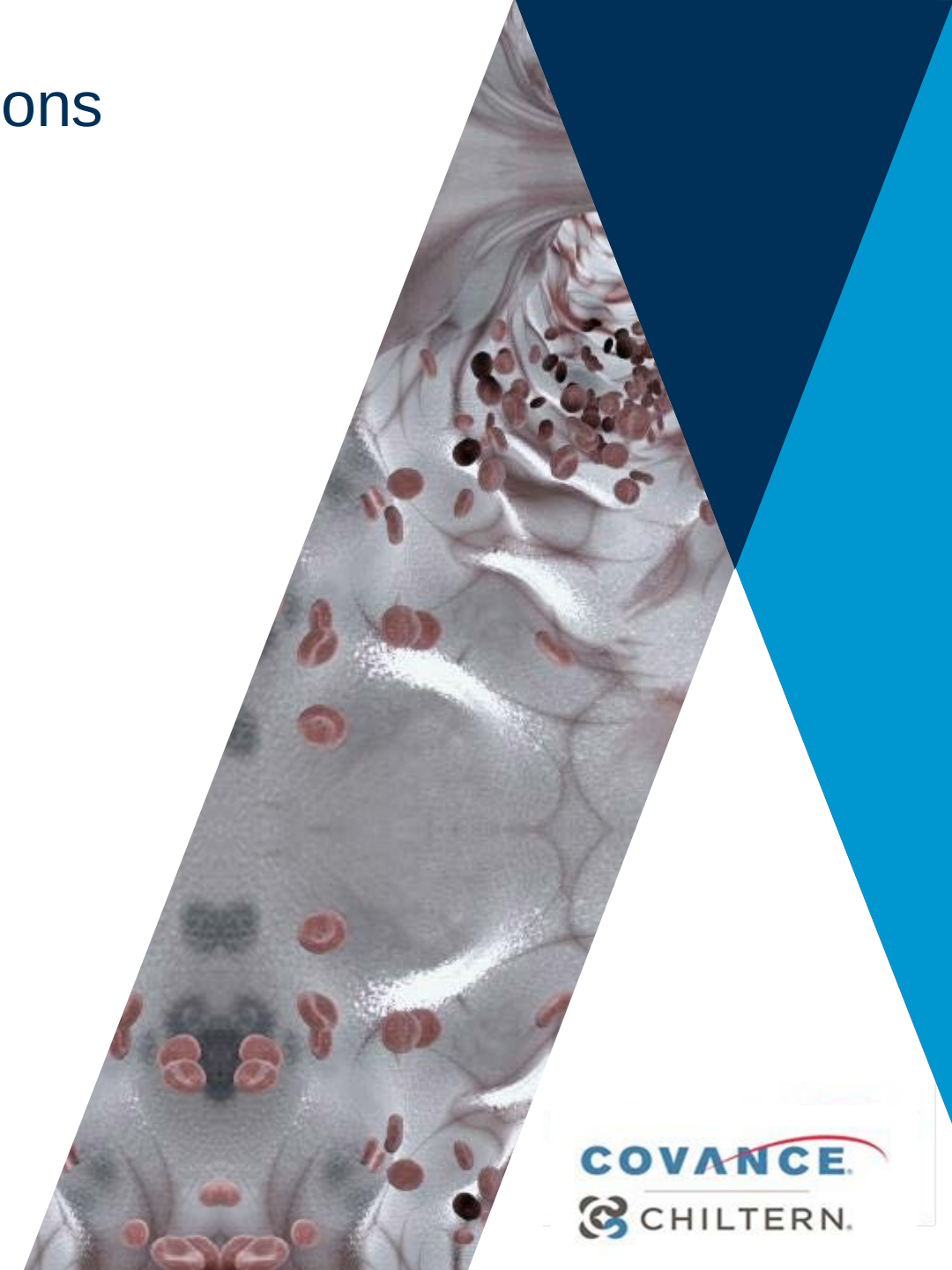
- Vendors
- AE/SAE
- Investigator Responsibilities
- Site Evaluation and Facility Tour

Welcome and Introductions



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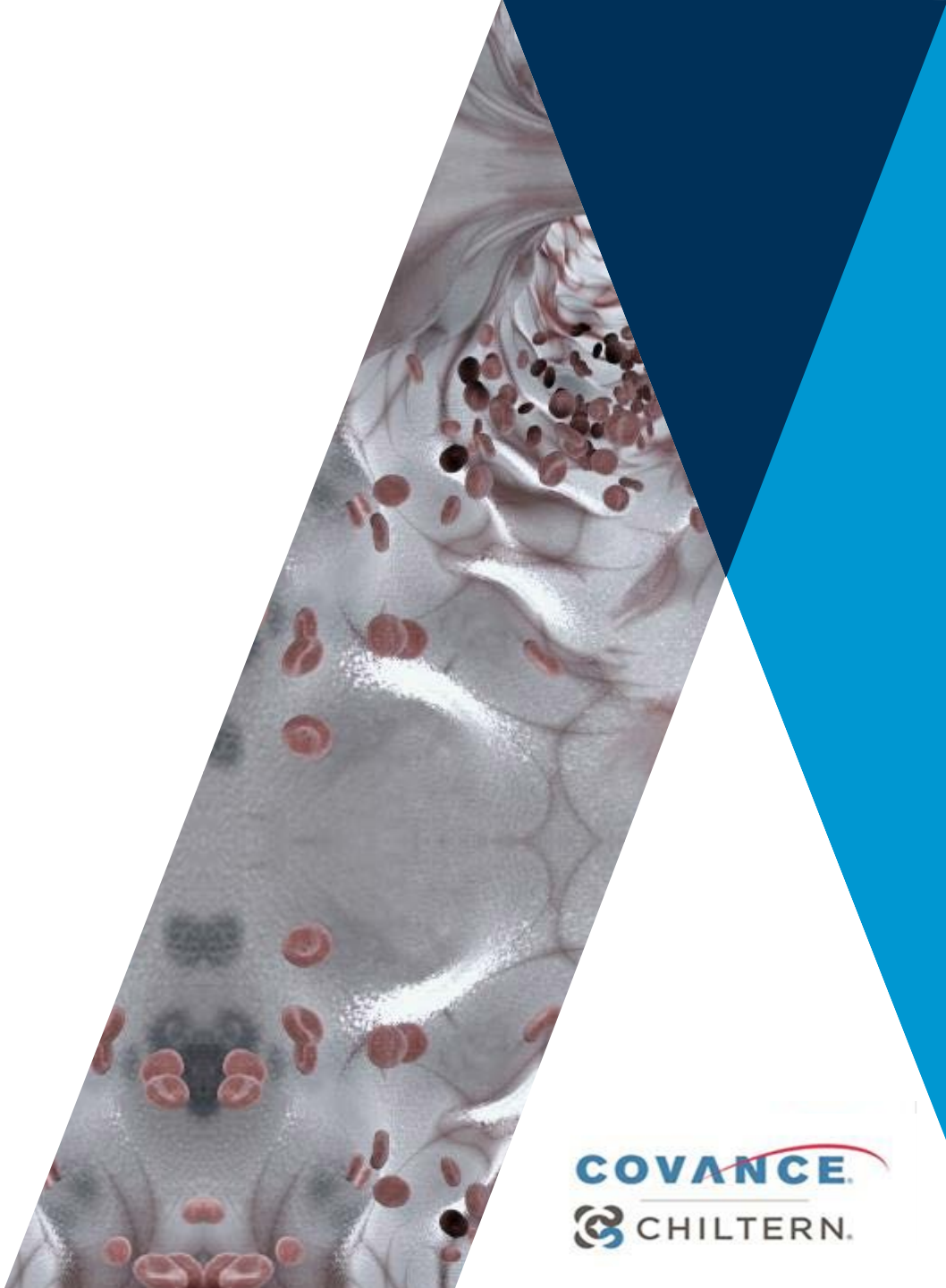
Study Timelines



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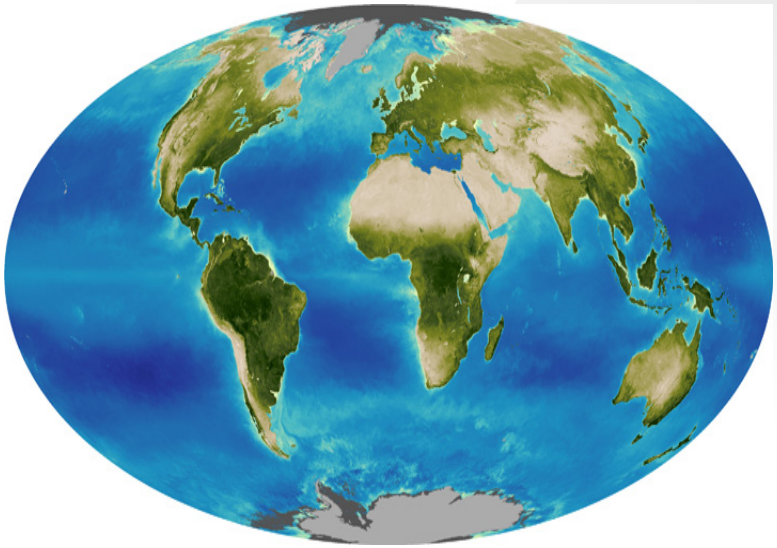
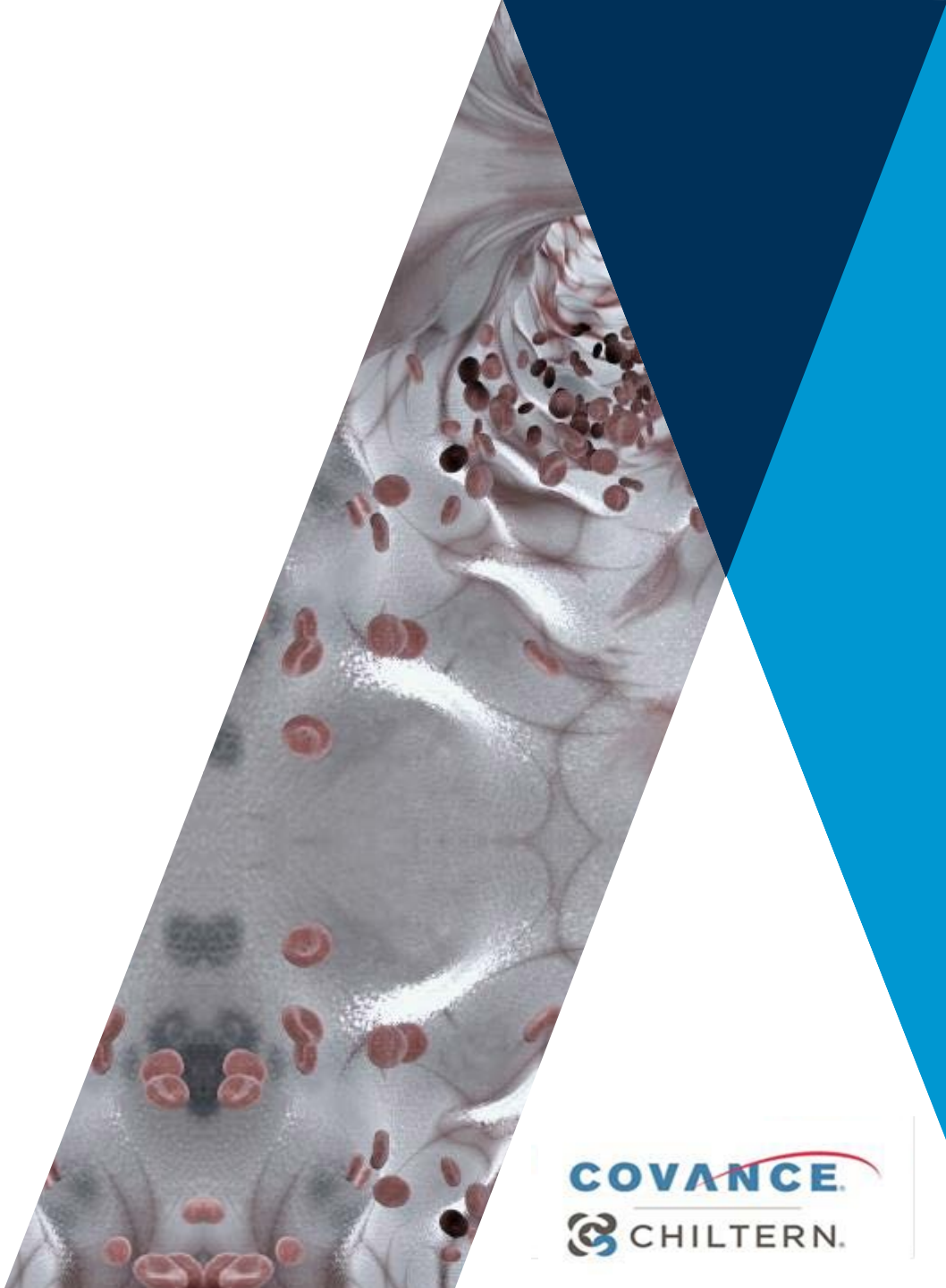
Timelines

Milestones	Dates
Pre Study Visits	April 2020
First Patient In (Screened)	30 June 2020
First Patient Dosed (Randomized)	25 July 2020

- Global Study: ~312 sites
- Screening: ~ 1000 patients
- Randomized: ~ 600 patients



Study Drug Overview



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Acalabrutinib

- also known as ACP-196
- is a highly selective, potent, **irreversible** small molecule **inhibitor of Bruton tyrosine kinase (BTK**)
- limited off-target kinase activity
- shows encouraging activity and acceptable safety in nonclinical and clinical studies
- 100 mg orally twice daily BID
- Calquence® has been approved in the United States and other markets for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy, chronic lymphocytic leukemia (CLL), and small lymphocytic lymphoma (SLL).
- BTK represents an important potential therapeutic target in DLBCL
  - BTK is an essential signaling molecule in the BCR pathway
  - A subset of ABC - DLBCL displays chronic active BCR signaling; These lymphomas die after knockdown of the BCR components IgM, CD79a, and CD79b and of kinases that transmit the BCR signal

Clinical data on BTK inhibition in DLBCL

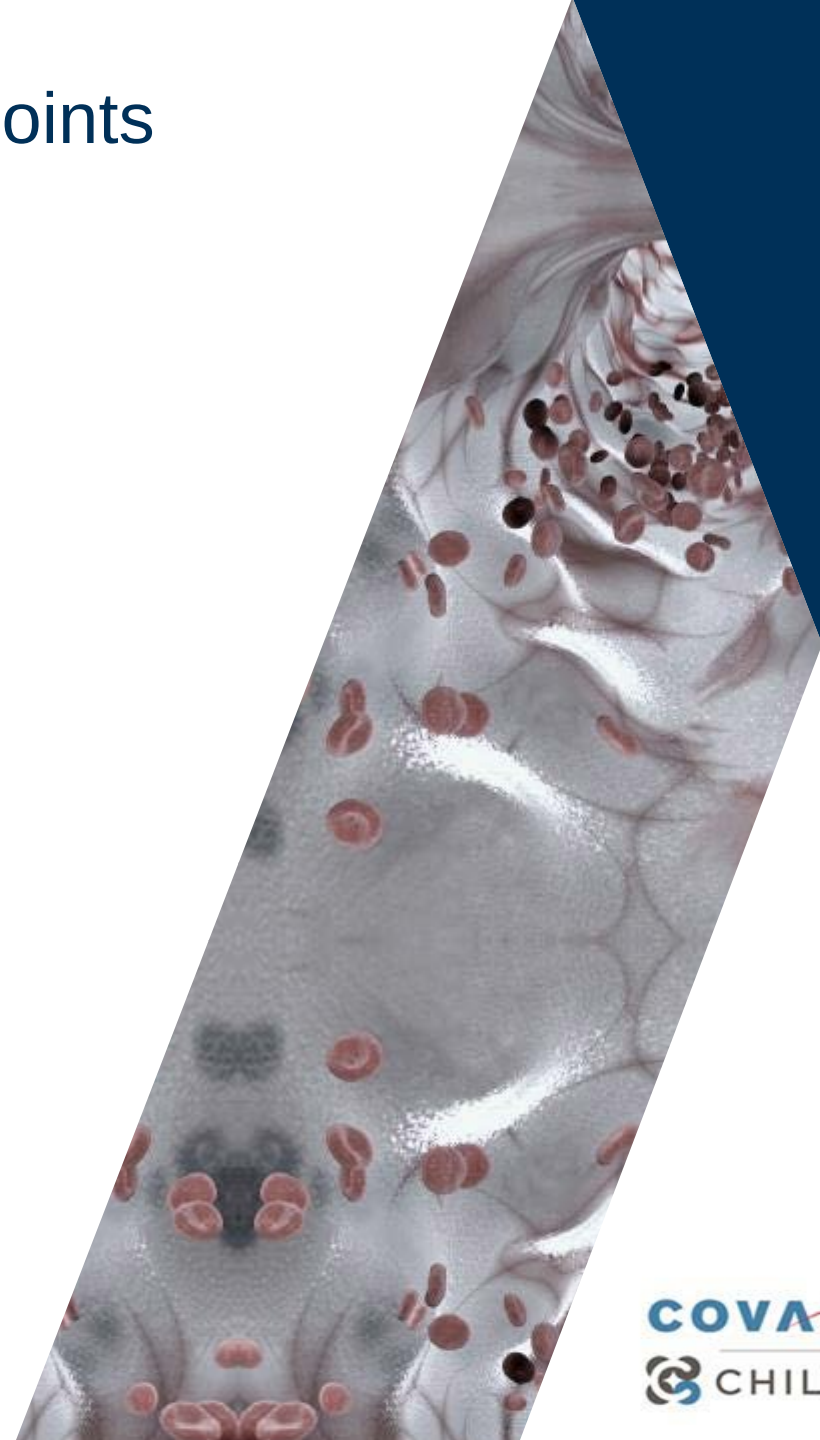
Ibrutinib

- In a Phase 2 study, **single-agen**t BTK inhibition with ibrutinib demonstrated anti-lymphoma activity against relapsed/refractory DLBCL (N=70), with less activity in the GCB subtype (overall response rate [ORR] 5%) compared with the unclassified (ORR 23%) or ABC (ORR 37%) subtypes .
- In the Phoenix **Phase 3** study in participants with non-GCB DLBCL, the EFS of **ibrutinib in combination with R-CHOP** was compared with R-CHOP alone in participants with previously untreated DLBCL. The study did not meet its primary endpoint of EFS. However, in a subgroup analysis of participants <65 years old, ibrutinib plus R-CHOP improved EFS, PFS and OS with manageable safety. Among participants aged ≥65 years, unexpected increased toxicity may explain in part the worse clinical benefit/risk profile for the ibrutinib-containing arm. The results from this study represent an area for further investigation.

Acalabrutinib

- Achieved a single-agent response rate of 24% in 21 patients with non-GCB DLBCL
  - 33% response rate in 9 patients with ABC DLBCL with a CR rate of 22% (2/9 pts)
- In the ACCEPT study acalabrutinib has been **combined with R-CHOP** in previously untreated DLBCL (all subtypes). Preliminary safety data (14 participants) demonstrated that acalabrutinib plus R-CHOP was overall well-tolerated.

Study Objectives / Endpoints



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Primary Objective / Endpoints

To compare acalabrutinib plus R-CHOP (AR-CHOP) relative to placebo plus R-CHOP (i.e., R-CHOP alone) in adult participants ≤65 years with previously untreated non-GCB DLBCL (ABC or unclassified) on progression free survival (PFS) based on investigator assessment

- PFS is defined as time from the date of first study intervention dosing (C1D1) until disease progression or relapse from CR (per 2014 Lugano Classification for NHL [Cheson et al 2014]) or death from any cause, whichever occurs first

Secondary Objectives / Endpoints

To compare AR-CHOP relative to R-CHOP on event-free survival (EFS)

- EFS is defined as the time from the date of first study intervention dosing (C1D1) until disease progression, relapse from CR, or initiation of subsequent systemic anti-lymphoma treatment and/or radiation after completion of 6 cycles of R-CHOP therapy, or death, whichever occurs first

To compare AR-CHOP relative to R-CHOP on CR rate at end of treatment by PET-CT, as determined by investigator and BICR

- CR rate is defined as the proportion of participants who achieve CR as best overall response per 2014 Lugano Classification for NHL

To compare AR-CHOP relative to R-CHOP on PFS as determined by BICR

- BICR-assessed PFS is defined as the time from the date of first study intervention dosing (C1D1) until disease progression or relapse from CR (per 2014 Lugano Classification for NHL [Cheson et al 2014]) or death from any cause, whichever occurs first

Secondary Objectives / Endpoints

To compare AR-CHOP relative to R-CHOP on PFS at the 3-year landmark, as determined by investigator and BICR

To compare AR-CHOP relative to R-CHOP on OS

- OS is defined as the time from first study dosing until the date of death from any cause

To evaluate the safety and tolerability of AR-CHOP in relation to R-CHOP

- AEs, SAEs, AESIs, Events of clinical interest, lab, AEs leading to discontinuation or study intervention dose modification; and vital signs, lab parameters, and ECGs

Secondary Objectives / Endpoints

PK of Acalabrutinib and its metabolite (ACP-5862)

- Summarized plasma concentrations of acalabrutinib and ACP-5862 at specified time points
- Pharmacokinetic parameters by population analyses as appropriate

Exploratory Objectives / Endpoints

To evaluate the efficacy of AR-CHOP compared with placebo plus R-CHOP in non-GCB participants as classified using methods other than GEP

- CR and PFS in non-GCB participants as classified using the investigational LymphMark Assay

To evaluate potential predictive biomarkers of response and resistance to the investigational study treatment

- Evaluation of predictive biomarkers and/or mechanisms of resistance

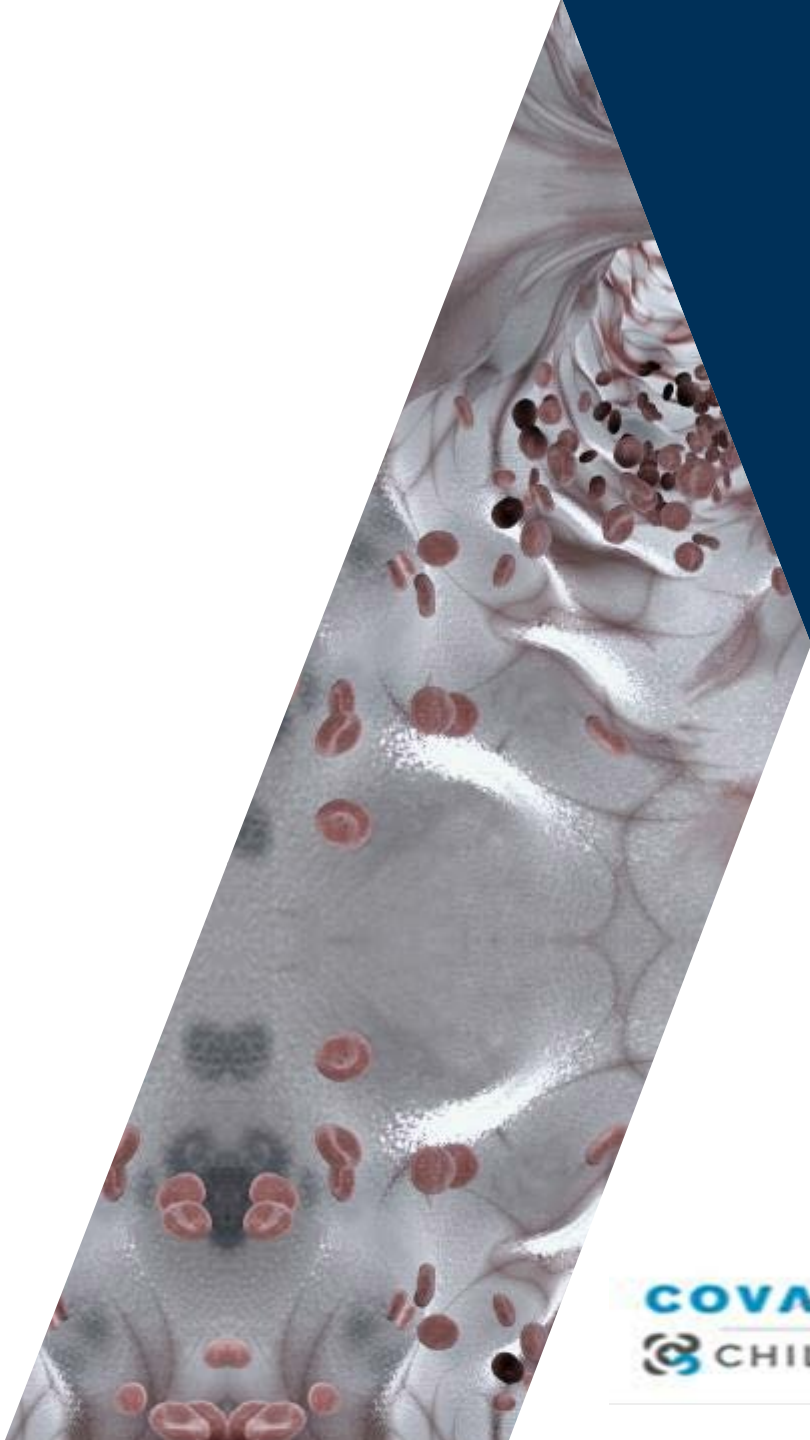
To assess minimal residual disease (MRD) detectability to understand depth of response from circulating tumor DNA (ctDNA) monitoring

- MRD negativity rate

To compare AR-CHOP relative to R-CHOP on patient-reported outcomes (PROs)

- HRQoL and FACT-Lym, NCI PRO-CTCAE, EQ-5D-5L, PGI-TT

Target Population



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Inclusion criteria (1/2)

Men and women ≥18 and ≤65 years of age

ECOG performance status of 0, 1, or 2

De novo DLBCL:

- Confirmation of DLBCL will be based on central review of the local pathology report
- Availability of archival or freshly collected tissue (FFPE samples) that must be sent to the central laboratory prior to first cycle of RCHOP for determination of the **non-GCB subtype** of DLBCL by GEP using the investigational LymphMark assay

No prior treatment for DLBCL

Measurable disease (≥1 lesion defined as ≥1.5 cm in the longest dimension for nodal lesions or ≥1 cm in the longest dimension for extranodal lesions as measured by CT with contrast (or MRI) per 2014 Lugano Classification (Cheson et al. 2014)

Revised International Prognostic Index (**RIPI) score of 2 to 5**.

Inclusion criteria (2/2)

Meet the following laboratory parameters:

- Adequate peripheral blood counts independent of growth factor or transfusion support during the screening period, as follows:
  - Absolute neutrophil count (ANC) ≥1.0×10^9/L (≥1,000/μL), except in the case of bone marrow involvement
  - Platelet count ≥75×10^9/L (≥75,000/μL), except in the case of bone marrow involvement when platelet count may be ≥50×10^9/L (≥50,000/μL)
  - Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 X ULN
  - Total bilirubin ≤ 1.5 X ULN, unless directly attributable to Gilbert syndrome
  - Estimated creatinine clearance of ≥40 mL/min, calculated using the Cockcroft and Gault equation or serum creatinine ≤2 X ULN

Left ventricular ejection fraction (LVEF) ≥55%, as determined by cardiac echocardiogram (ECHO) or multiple-uptake gated acquisition (MUGA) scan

Exclusion criteria (1/3)

Known history or presence of CNS lymphoma or leptomeningeal disease

Known primary mediastinal lymphoma

Prior history of indolent lymphoma

Known history of a bleeding diathesis (i.e., hemophilia, von Willebrand disease)

History of or ongoing confirmed progressive multifocal leukoencephalopathy

Major surgical procedure within 30 days before first dose of study drug.

Contraindication to any of the individual components of CHOP

History of prior malignancy that could affect compliance with the protocol or interpretation of results, except for the following:

- Curatively treated basal cell carcinoma or squamous cell carcinoma of the skin or carcinoma in situ of the cervix at any time prior to study
- Malignancy treated with curative intent and with no known active disease present for ≥3 years before randomization

Significant cardiovascular disease such as symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months before screening or any Class 3 or 4 NYHA.

Exclusion Criteria (2/3)

Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach; extensive small bowel resection that is likely to affect absorption, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction; or gastric restrictions and bariatric surgery, such as gastric bypass.

Known history of infection with HIV

Any active uncontrolled systemic infection

Serologic status reflecting active hepatitis B or C infection

- Subjects who are hepatitis B core antibody (anti-HBc) positive and hepatitis B surface antigen (HBsAg) negative are required to have a negative hepatitis B DNA PCR result
- Subjects who are hepatitis C antibody positive are required to have a negative hepatitis C RNA PCR result

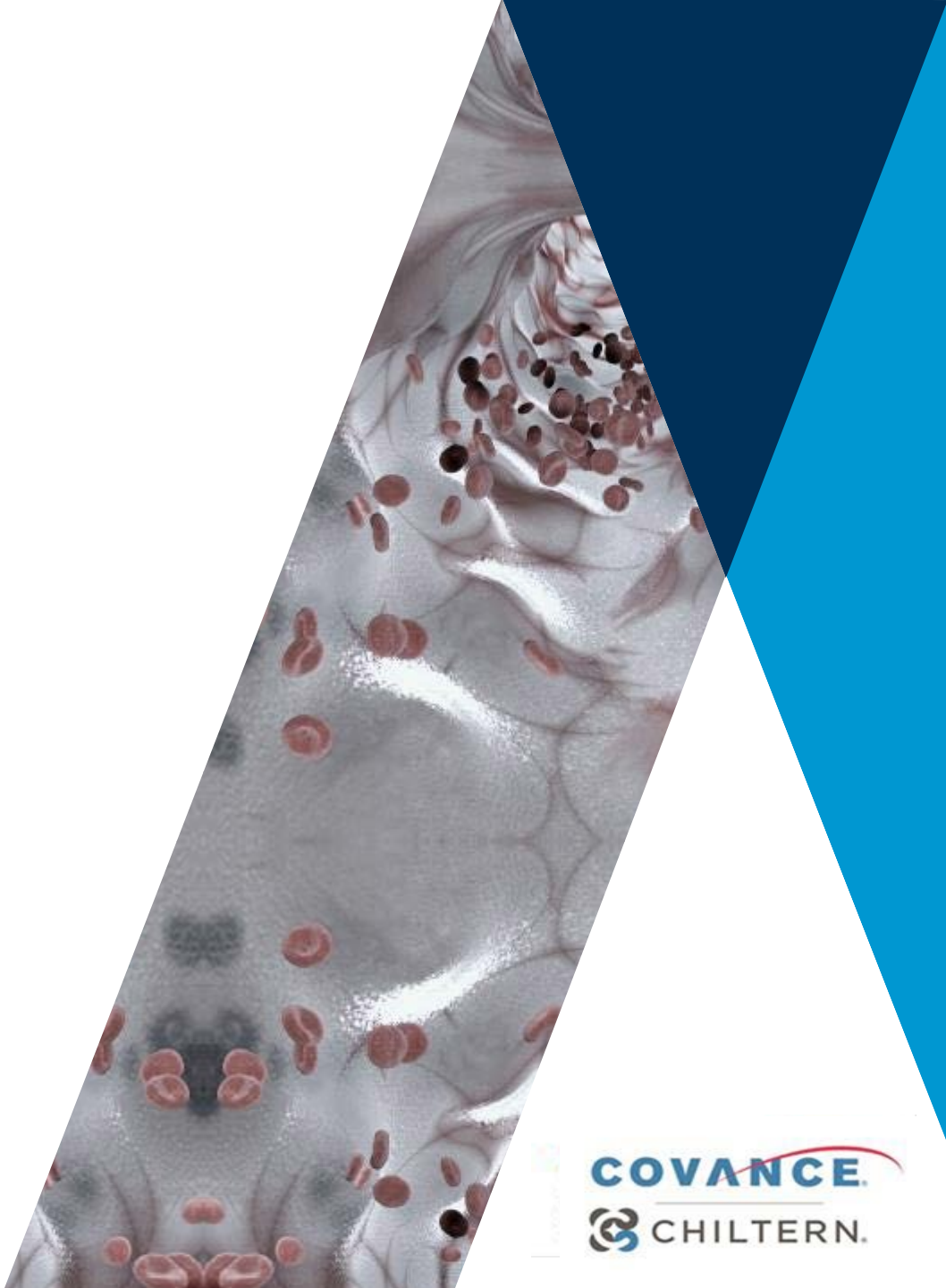
History of known hypersensitivity or anaphylactic reactions to study drugs or excipients.

History of stroke or intracranial hemorrhage within 6 months before first dose of study drug

Exclusion criteria (3/3)

- Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists
- Requires continued treatment with a strong cytochrome P450 3A (CYP3A) inhibitor
- Requires treatment with proton pump inhibitors (i.e., omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole or pantoprazole). Subjects receiving proton pump inhibitors who switch to H2-receptor antagonists or antacids are eligible for enrollment to this study.
- Received a live virus vaccination within 28 days before the first dose of study drug
- Breastfeeding or pregnant
- Concurrent participation in another therapeutic clinical trial

Study Design



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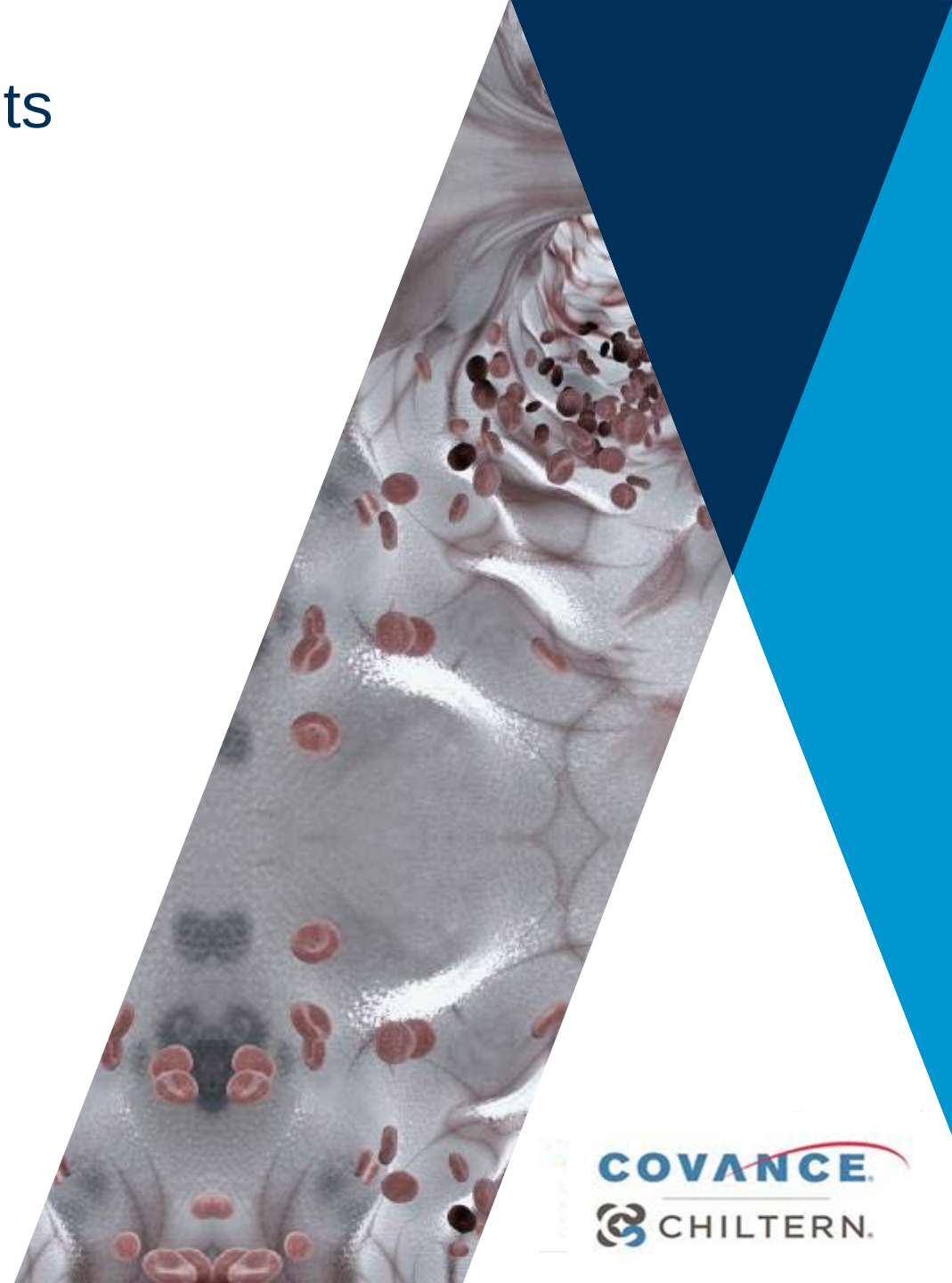
Study Design

- ✓ A Phase 3, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of acalabrutinib plus R-CHOP (AR-CHOP) compared with placebo plus R-CHOP
- ✓ Participants ≤65 years with previously untreated non-GCB DLBCL (ABC and unclassified)
- ✓ The treatment period: 8 treatment cycles; each cycle is 21 days.
- ✓ Randomization 1:1 stratified by the following factors: Geographic region (Asia versus US/Canada/Western Europe/Oceania versus Rest of World) and R-IPI score (2 [good prognosis] versus 3–5 [poor prognosis])
- ✓ 2 study arms: Prior to randomization, all enrolled participants will receive an initial cycle of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone R-CHOP (Cycle 1) as part of standard of care treatment.

- **Arm A + Arm B**: Total of 8 treatment cycles as follows:
  - Cycle 2 through Cycle 6: R-CHOP
  - Cycle 7 through Cycle 8: Rituximab
  - Cycle 2 through Cycle 8: Acalabrutinib 100 mg BID (Arm A), Placebo BID (Arm B)

Schedule of Assessments



Schedule of Assessments

Pre-Randomization (SCR + C1)

- Screening Part 1 (Pre-enrollment): Days -30 to -1
- Screening Part 2 / SoC treatment (Post-enrollment) Cycle 1: Day 1 to Day 21

Post-Randomization (C2 – C8)

- Cycle 2 to 6 (Day 1 ±2 days)
- Cycle 7 to 8 (Day 1 ±2 days)

Post-Treatment

- EOT Response Assessment / Safety Follow-Up: 30 days from last dose (+7 days)
- Post-Treatment Disease Follow-Up: Q4M (through Year 3) (±7 days), Q6M (Year 4 through Year 5) (±10 days)
- Survival Follow-Up: Q6M (±7 days)

Study Procedures: Biopsy

Screening Pre-enrollment: Days –30 to -1

Enrollment Procedures

FFPE (formalin-fixed, paraffin-embedded) **tumor biopsy** and local pathology report collection **for central laboratory determination of the non-GCB subtype** of DLBCL and for verification of DLBCL diagnosis is required before a participant is considered eligible for randomization.

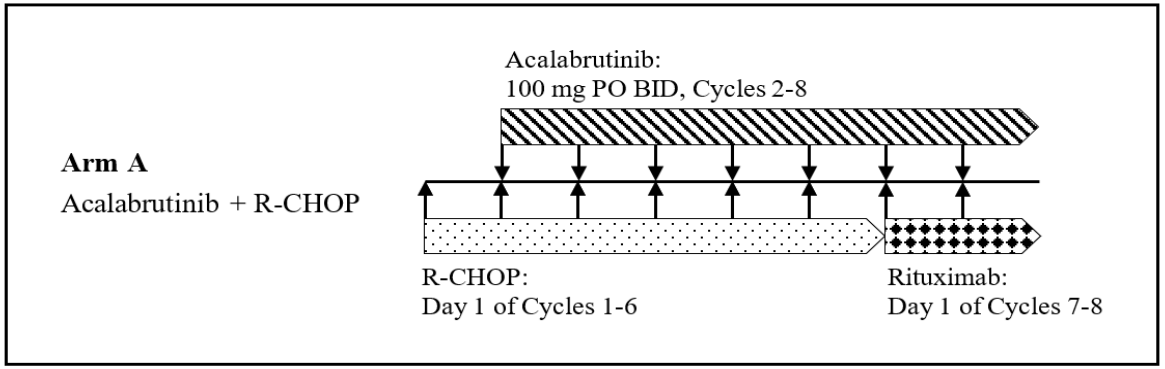
- Sample must be sent to the central testing laboratory within 28 days before first cycle of R-CHOP
- a biopsy extracted from a participant >28 days prior to R-CHOP is permitted.
- central laboratory gene expression profiling (GEP) testing to determine cell of origin (COO) status
- COO test results confirming non-GCB DLBCL are required prior to randomization and to begin investigational study intervention (C2D1).
- Bone marrow is not sufficient for confirmation of the non-GCB subtype.
- Part of the tumor biopsy will be used for biomarker studies.

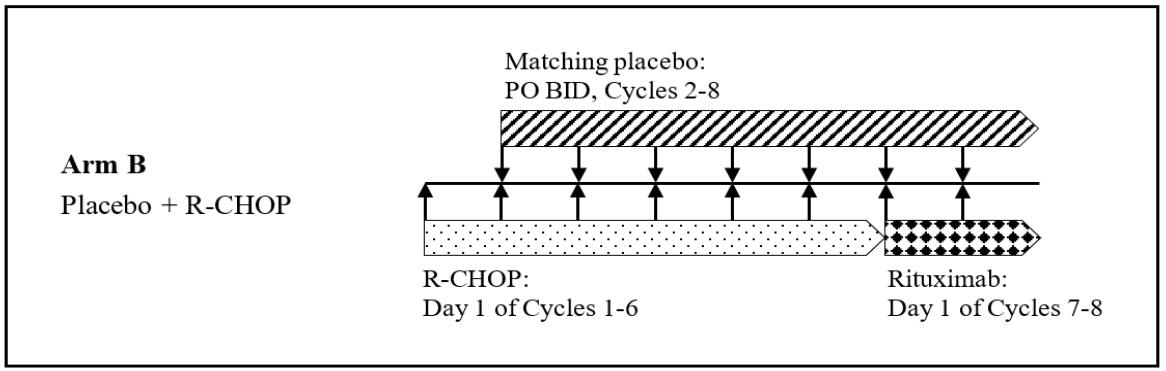
A bone marrow aspirate and biopsy sample will be collected at screening (an archival sample may be used if collected ≤12 weeks before randomization). If bone marrow involvement at screening, a repeat biopsy at EOT is mandatory to confirm a CR.

Disease Evaluations

Tumor assessment with FDG-PET/CT and CT with contrast will be required at	• screening (within 30 days of Cycle 1 Day 1 of R-CHOP therapy) • after Cycle 4 Day 21/prior to Cycle 5 Day 1 • 30 days (+7) after the end of Cycle 8.
In the follow-up period diagnostic CT scans with contrast (without PET scans)	•every 4 months for the next 3 years •then every 12 months through Year 5 •then only as clinically indicated at the discretion of the investigator •Any time the investigator suspects disease progression •MRI may be used instead of CT scans with contrast in patients for whom CT scans with contrast are contraindicated. •The results of PET-CT and CT scans performed outside of these scheduled timepoints should be recorded on the eCRF.
Bone marrow (aspirate/biopsy)	• Screening • EOT visit if involvement at screening
FACT-Lym, EQ-5D-5L, NCI-PRO-CTCAE, PGI-TT	•During pre- and post-randomization phases •Baseline ePROs should be completed by participants before dosing at Cycle 1 Day 1. •In the post-treatment phase participants will switch to providing site-based PRO assessments during follow-up visits.

Dosing





- **Acalabrutinib:** 100 mg/Placebo orally, twice per day
- **Rituximab:** 375 mg/m2 intravenous infusion on Day 1
- **Cyclophosphamide:** 750 mg/m2 intravenous infusion on Day 1
- **Doxorubicin:** 50 mg/m2 intravenous infusion on Day 1
- **Vincristine:** 1.4 mg/m2 intravenous infusion on Day 1
- **Prednisone (or equivalent):** 100 mg orally, once daily on Days 1 to 5

Dosing cont.

Acalabrutinib/Placebo

- Administration begins on Cycle 2 Day 1 and continues through Cycle 8 (C8D21), unless the participant experiences unacceptable toxicity or disease progression.
- Recommended to take Acalabrutinib/Placebo 100 mg capsules as close to the scheduled time as possible (approx. 12 hours apart, preferably within ±1 hour).
- If a dose is missed, it can be taken **up to 3 hours** after the scheduled time, with a return to the normal schedule upon the following dose.
- Acalabrutinib/Placebo can be taken **with or without food.** Capsules will be taken with **8 ounces (approximately 240 mL) of water**. The capsules should be swallowed intact and participants should not attempt to open capsules or dissolve them in water. Caution against using herbal remedies or dietary supplements unless approved by the study physician
- Acalabrutinib/Placebo should be administered **approximately 1 hour prior to R-CHOP.**

Dosing cont.

Rituximab (375 mg/m2)

- **An IV infusion on Day 1 of each 21-day cycle**, for a maximum of 8 cycles
- Rituximab will be administered **before chemotherapy (CHOP)** and can be given no later than 72 hours after CHOP. It should not be administered as an IV push or bolus.
- Consideration should be given to withholding antihypertensive medications for 12 hours before rituximab infusion due to potential transient hypotension during rituximab infusion
- **Premedication** consisting of acetaminophen, diphenhydramine (or other suitable antihistamine), and a single dose of hydrocortisone (up to 100 mg or an equivalent dose of methylprednisolone) also may be administered **beginning with the first infusion**.
- **First infusion** (Cycle 1 Day 1): initial rate of 50 mg/h. If no infusion-related or hypersensitivity reaction, increase the infusion rate in 50-mg/h increments every 30 minutes, to a maximum of 400 mg/h. If an IRR develops, stop/slow the infusion and administer infusion-reaction medications and supportive care. Once the reaction resolves, resume the infusion at a 50% reduction in rate
- **Subsequent infusions:** If infusion-related or hypersensitivity reaction during the prior infusion, begin infusion at an initial rate of 50 mg/h and follow instructions for the first infusion. If the participant tolerated the prior infusion well (defined as an absence of Grade 2 reactions during a final infusion rate of ≥100 mg/h), begin the infusion at a rate of 100 mg/h. If no infusion reaction occurs, increase the infusion rate in 100-mg/h increments every 30 minutes, to a maximum of 400 mg/h. If an IRR develops, stop or slow the infusion and administer infusion-reaction medications and supportive care. If the reaction resolves, resume the infusion at a 50% reduction in rate.

Dosing cont.

Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (or Equivalent)

- **Cyclophosphamide (750 mg/m2):** an IV infusion over 20 to 60 minutes on Day 1 of each 21-day cycle, for a maximum of 6 cycles
  - During and immediately after cyclophosphamide administration, adequate amounts of fluid should be ingested or infused to force diuresis to reduce the risk of urinary tract toxicity.
- **Doxorubicin (50 mg/m2):** an IV bolus on Day 1 of each 21-day cycle, for a maximum of 6 cycles
  - The recommended lifetime cumulative dose limit of doxorubicin is 450 to 550 mg/m2. The maximum dose given for each participant in this study will be 300 to 400 mg/m2, depending on the number of cycles given.
- **Vincristine (1.4 mg/m2):** an IV infusion (administered over 15 minutes) on Day 1 of each 21-day cycle, for a maximum of 6 cycles
  - The upper limit for each 1.4-mg/m2 dose is 2 mg, regardless of BSA, to limit the risk of neurotoxicity
- **Prednisone (100 mg** or equivalent): orally on Days 1 to 5 of each cycle and should be taken **in the morning with food prior to the rituximab infusion**. Prednisone may be replaced with prednisolone (1:1 conversion) in countries where prednisone is not available or is not the therapy of choice.

Dosing cont.

The order of administration of study interventions on Day 1 of each cycle: first prednisone, second rituximab, subsequent infusions of cyclophosphamide, vincristine, and doxorubicin should be administered per institutional guidelines.

Cycle	Standard of Care Treatment	Dose
C1	Rituximab	375 mg/m^2 IV on Day 1
	Cyclophosphamide	750 mg/m^2 IV on Day 1
	Doxorubicin	50 mg/m^2 IV on Day 1
	Vincristine	1.4 mg/m^2 IV on Day 1
	Prednisone (or equivalent)	100 mg PO QD on Days 1–5
Cycle	**Investigational Study Treatment**	**Dose**
C2 – C8	Acalabrutinib/matching placebo	100 mg PO BID (1×100 mg capsule every 12 hours)
	Rituximab	375 mg/m^2 IV on Day 1
C2 – C6	Cyclophosphamide	750 mg/m^2 IV on Day 1
	Doxorubicin	50 mg/m^2 IV on Day 1
	Vincristine	1.4 mg/m^2 IV on Day 1
	Prednisone (or equivalent)	100 mg PO QD on Days 1–5

BID=twice daily; IV=intravenous; PO=oral; QD=once daily; R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

Note: All treatment cycles are 21 days. Treatment with R-CHOP and acalabrutinib/matching placebo will begin at Cycle 2 Day 1.

Concomitant Therapy / Additional restrictions

Required Concomitant Therapy

- Primary Prophylactic Hematopoietic G-CSFs (i.e., pegfilgrastim or filgrastim) is required as primary prophylaxis (within 24 to 72 hours after R-CHOP administration) and must be continued through subsequent cycles of chemotherapy for all randomized participants, unless contraindicated or otherwise not tolerated.

Permitted Concomitant Therapy

- Standard supportive care medications are permitted; this includes premedication to decrease the risk of tumor lysis syndrome (TLS), IRR, infections, CNS prophylaxis, and other risks or toxicities.
- Transfusions of packed red blood cells or platelets are permitted at the discretion of the investigator. All transfusions should be leukopore-filtered and irradiated.
- Infection prophylaxis may be indicated

Monitoring and Management of TLS

- Participants be monitored for at least 24 hours after the administration of the final agent of the first cycle. If rasburicase is not used in the initial management of the participant, electrolyte levels should be determined 8 hours after chemotherapy, which may require a 1-night hospital stay.
- The best management of TLS is prevention. Adequate hydration and urine output.

Drug-Drug Interactions

- Acalabrutinib is metabolized by CYP3A, randomized participants should be strongly cautioned against the use of herbal medication or dietary supplements (in particular, St John's wort, which is a potent CYP3A inducer).
- The concomitant use of strong inhibitors/inducers of CYP3A with acalabrutinib/placebo should be avoided when possible. If a participant requires short-term treatment with a strong CYP3A inhibitor (such as anti-infectives for up to 7 days), interrupt acalabrutinib/placebo treatment. When acalabrutinib/placebo is co-administered with moderate CYP3A inhibitors, reduce acalabrutinib/placebo dose to 100 mg once daily (QD).
- Avoid co-administration of strong CYP3A inducers. If a participant requires treatment with a strong CYP3A inducer, increase the acalabrutinib/placebo dose to 200 mg BID during concomitant administration with the strong inducer and return to recommended dose of 100 mg BID after stopping the strong CYP3A inducer.
- Use of proton-pump inhibitors, H2-receptor antagonists, or antacids while taking acalabrutinib has the potential to decrease acalabrutinib exposure. If treatment with a gastric acid reducing agent is required, consider using a H2-receptor antagonist (2 hours after acalabrutinib/placebo) or antacid (2 hours before or 2 hours after acalabrutinib/placebo). Avoid co-administration with proton pump inhibitors.

Dose Modification/Delay/Discontinuation

- If any one of the R-CHOP components is delayed due to toxicity, all components should be delayed for **up to 3 weeks** (21-day dosing interval should be maintained for R-CHOP regardless of dose delay). Acalabrutinib/placebo should be held during the R-CHOP delay phase.
- If toxicity persists after a 3-week cycle delay that is related to 1 or more specific drugs (e.g., vincristine, doxorubicin, etc.), the offending drug(s) should be discontinued and the new cycle should be started with the remaining drugs.
- A participant whose cycle is delayed should be **assessed weekly** for resolution of toxicity
- If there is a delay in the start of a new cycle of more than 3 weeks due to insufficient recovery from toxicity (with all drugs withheld), participants will discontinue study treatment.

Dose Modification/Delay/Discontinuation

Acalabrutinib / Placebo

- If the dose of acalabrutinib is reduced for apparent treatment-related toxicity, the dose does not need to be re-escalated, even if there is minimal or no toxicity with the reduced dose.
- If the participant tolerated a reduced dose of acalabrutinib for ≥3 weeks, then the dose may be increased to the next higher dose level, at the discretion of the investigator.
- Participants who discontinue any component of R-CHOP without disease progression will continue acalabrutinib/placebo until the completion of Cycle 8, disease progression, or unacceptable toxicity, whichever occurs first.
- If acalabrutinib/placebo is delayed or withheld, any remaining study intervention (i.e., rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [or equivalent]) may be continued.

Dose Modification Guidelines for Acalabrutinib/Placebo

Occurrence	Action
1st	Hold acalabrutinib/placebo until recovery to Grade 1 or baseline; may restart at original dose level
2nd	Hold acalabrutinib/placebo until recovery to Grade 1 or baseline; restart at one dose level lower (100 mg QD)
3rd	For nonhematologic AEs, discontinue acalabrutinib/placebo. For thrombocytopenia with significant bleeding, discontinue acalabrutinib/placebo. For other hematologic AEs, upon recovery to Grade 1 or baseline, restart at 100 mg QD.
4th	For hematologic AEs, discontinue acalabrutinib/placebo

The actions in table above should be taken for the following drug-related toxicities:

- ❑ Grade ≥3 neutropenia with infection or fever
- ❑ Grade 4 neutropenia (ANC <0.5×109/L [i.e., <500/μL] for >7 days
- ❑ Grade 3 thrombocytopenia (platelets <50×109/L [i.e., <50,000/μL]) in the presence of significant bleeding (i.e., Grade ≥2 bleeding)
- ❑ Grade 4 thrombocytopenia (platelets <25×199/L [i.e., <25,000/μL])
- ❑ Any Grade ≥3 non-hematological toxicity

Dosing Interruption/Modifications- AE Management

Rituximab

- No dose modifications of rituximab (375 mg/m2) are allowed
- Rituximab should be held for any Grade 4 toxicity or for any rituximab-related, clinically significant, unmanageable Grade 3 AEs, until the AE returns to baseline or resolves completely

Cyclophosphamide

- Dose adjustments for cyclophosphamide should follow the local prescribing information.
- If participants' blood counts do not meet the lab parameters for hemoglobin, ANC, and platelets, the treatment will be delayed.
- The most common AEs are hematological toxicities; myelosuppression with leucopenia, anemia, and thrombocytopenia. Hemorrhagic cystitis and hematuria can occur and may necessitate interruption of dosing. Prophylaxis for hemorrhagic cystitis can be used per local prescribing information and institutional standard of care.

Dosing Interruption/Modifications- AE Management

Doxorubicin

- Dose adjustments for doxorubicin should follow the local prescribing information.
- Dose-limiting toxicities of doxorubicin therapy are mucositis, myelosuppression, and cardiotoxicity.
- Cardiotoxicity as an arrhythmia may occur directly after administration and ECG changes may last up to 2 weeks after administration. Cardiotoxicity may, however, occur several weeks or months after administration.
- Doxorubicin is metabolized by the liver and excreted in bile. Impairment of liver function results in slower excretion of the drug and consequently increased retention and accumulation in the plasma and tissues, resulting in enhanced clinical toxicity. Doxorubicin dosage should be reduced if hepatic function is impaired.

Dosing Interruption/Modifications- AE Management

Dose Modification and Guidance for Cyclophosphamide and Doxorubicin Hematological Toxicities

ANC	Platelet Count	Dosage and Guidance
≥1,000/µL	≥75,000/µL	100% of the designated dose
≥500/µL and no febrile neutropenia	≥50,000/µL	100% of the designated dose after recovery of ANC to ≥1,500/µL and platelets to ≥100,000/µL
<500/µL and/or febrile neutropenia (ANC <500/µL + fever ≥38.5°C)	N/A	Initiation of G-CSF for all subsequent cycles is recommended
<500/µL and/or febrile neutropenia (ANC <500/µL + fever ≥38.5°C despite growth factors)	<50,000/µL	25% dose reduction for subsequent cycles
Recurrence of <500/µL and/or febrile neutropenia (ANC <500/µL + fever ≥38.5°C despite growth factors)	Second episode of <50,000/µL	Additional 25% dose reduction for subsequent cycles
Third episode of <500/µL and/or febrile neutropenia (ANC <500/µL + fever ≥38.5°C despite growth factors and 2 dose reductions)	Third episode of <50,000/µL	Discontinue

Dosing Interruption/Modifications- AE Management

Vincristine

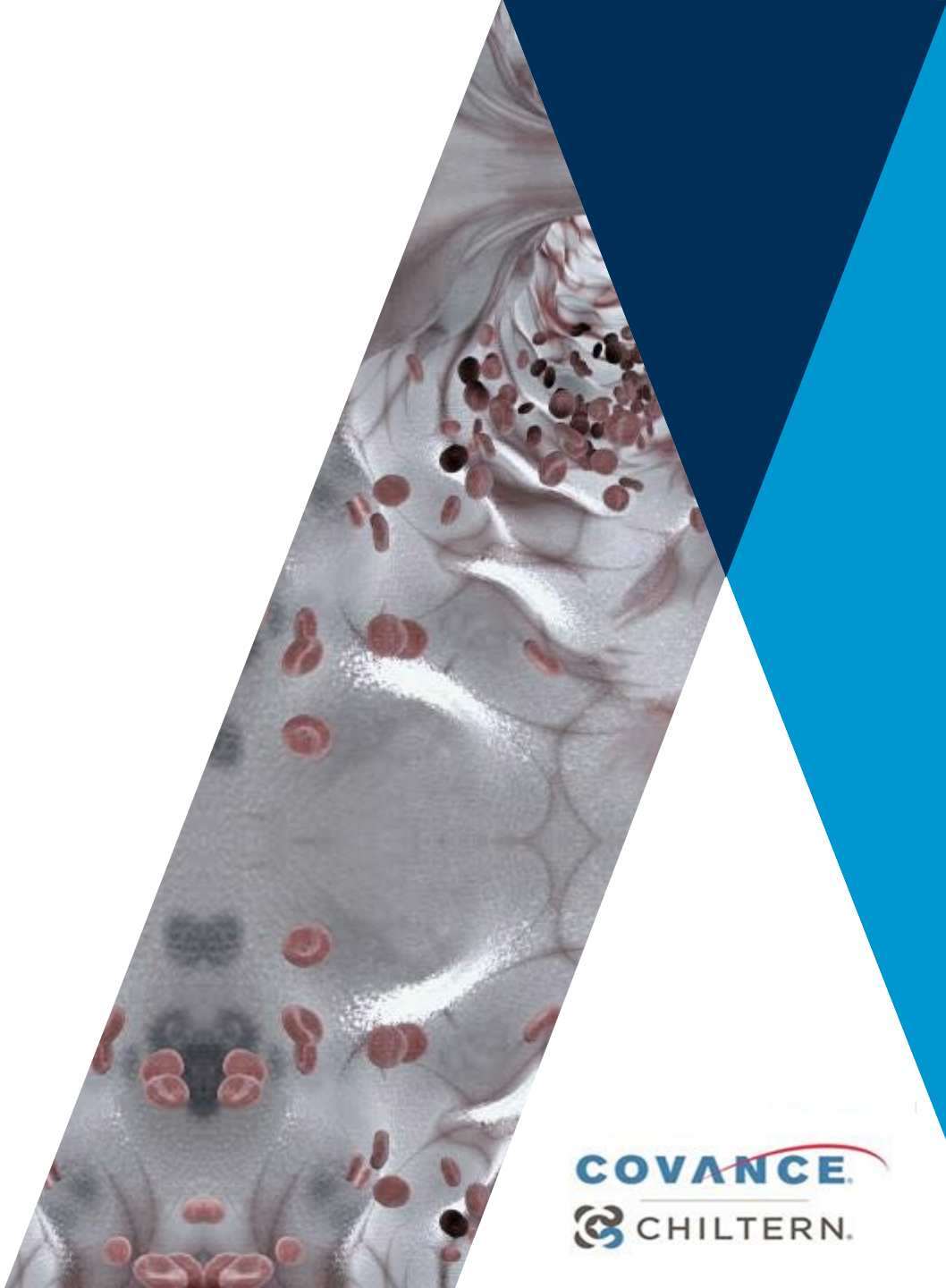
- Dose adjustments for vincristine should follow the local prescribing information.
- The vincristine dosage should be reduced if hepatic function is impaired. Vincristine doses should be re-escalated when hyperbilirubinemia improves.
- In case of severe neurotoxicity (Grade 3), vincristine should not be administered, especially if there are signs of paresthesia or paresis. Treatment may be resumed at 50% of the dose when symptoms subside.
- Vincristine should be reduced by 25% for any episode of ileus/constipation requiring hospitalization. Vincristine should be permanently discontinued for Grade 4 neuropathy of any type.
- There are no established recommended agents for the prevention of CIPN in patients with cancer undergoing treatment with neurotoxic agents. For patients experiencing CIPN, clinicians may offer duloxetine or follow standard practice.

Dosing Interruption/Modifications- AE Management

Prednisone (or Equivalent)

- Dose adjustments for prednisone (or equivalent) should follow the local prescribing information.
- Relatively higher risk of developing or exacerbating some conditions (e.g., bacterial infections, viral infections, systemic mycoses, hypertension, diabetes mellitus, and gastrointestinal conditions such as peptic ulcers, pancreatitis, and diverticulitis).
- If AE related to prednisone or equivalent, the dose should be adjusted to a level specific to that participant but should be no less than 80 mg per day
- In exceptional circumstances, a participant may not tolerate sudden steroid withdrawal after 5 days of prednisone or equivalent therapy. In such an instance, a tapering regimen of prednisone (or equivalent) is indicated.

Vendors



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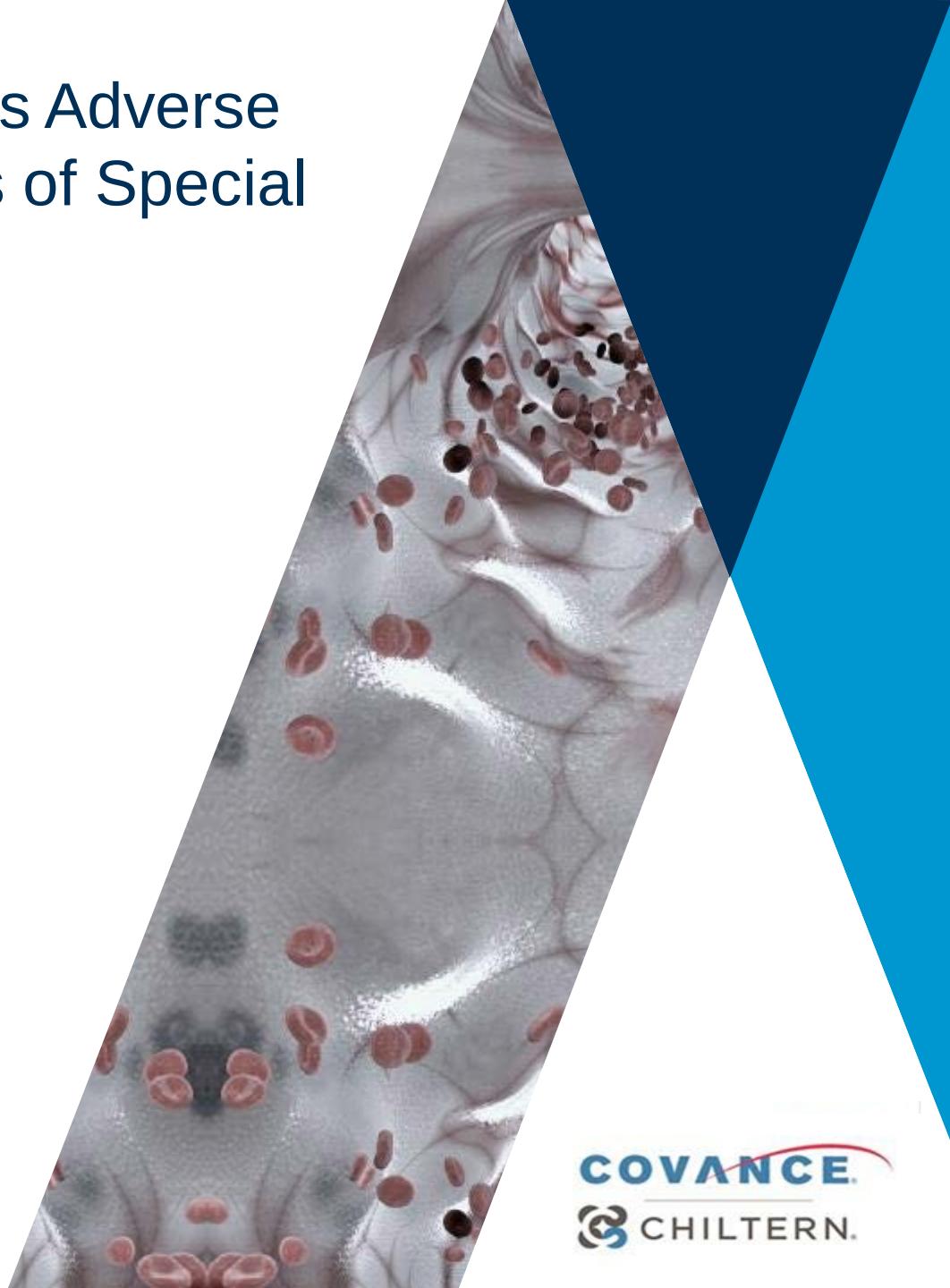
Vendors

Service	Vendor
Imaging	Parexel
Central Lab	Covance
Clinical bioanalysis	Covance Bioanalysis
Fischer	IMP Supply
ECG, Spirometry, ePRO	E Research Technology (ERT)
IXRS	Perceptive (Parexel) - R-CHOP, Acalabrutinib and G-CSF to be provided by sponsor and managed thru IXRS
Translations	Transperfect/Telelinqua
EDC – RAVE	Medidata
PharmaSpecific	Patient Reimbursement – France
Sermes	Patient Reimbursement – Spain

Adverse Events / Serious Adverse Events / Adverse Events of Special Interest



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Reporting **no later than 24 hours** after learning of the event

- All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s).
- The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- All AEs associated with an overdose or incorrect administration
- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy

Once the investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated sponsor representative. If the EDC system is not available, then the investigator or other study site staff reports a SAE to the appropriate sponsor representative by telephone. The sponsor representative will advise the investigator/study site staff how to proceed.

Adverse Events of Special Interest (AESIs)

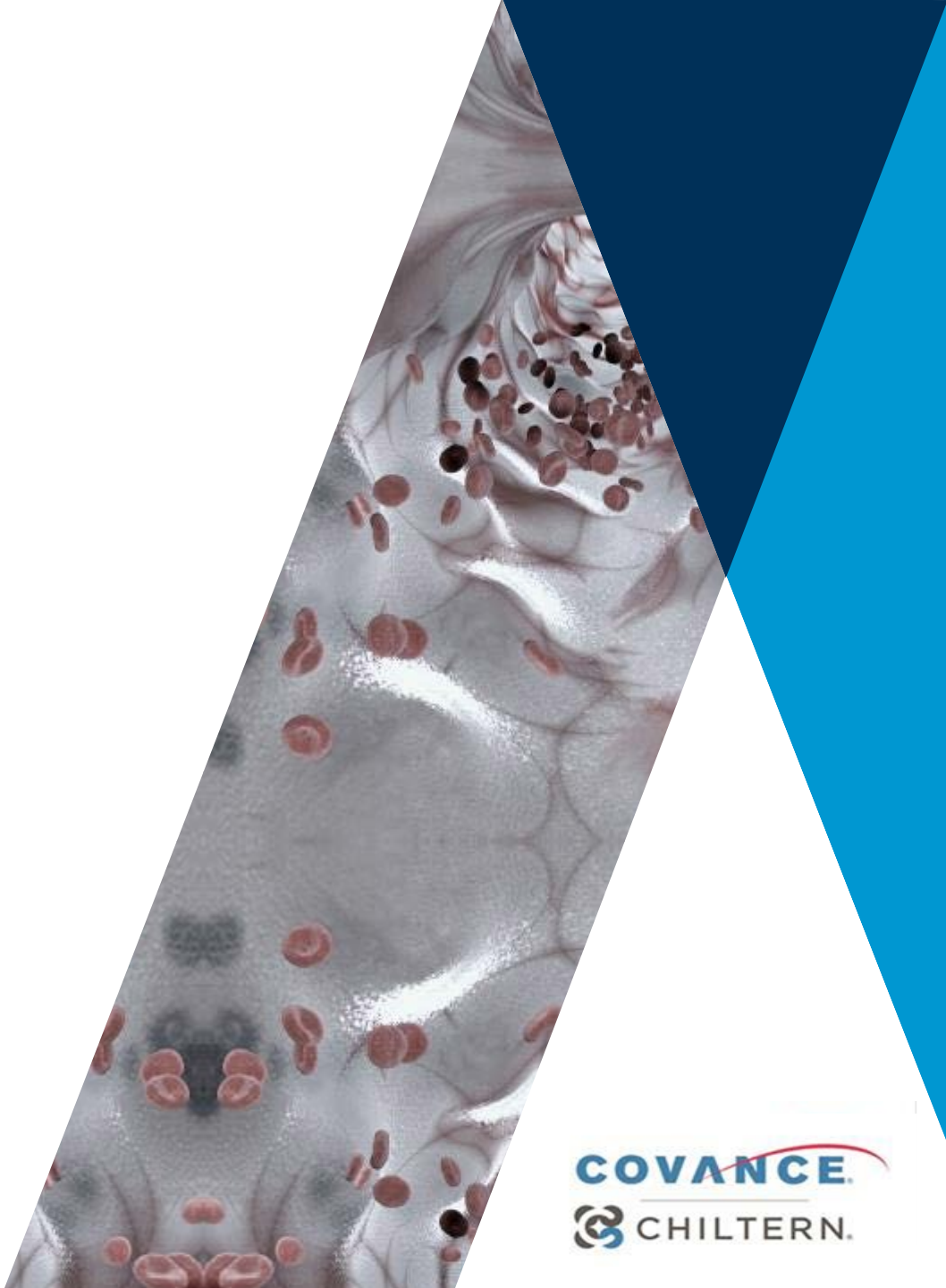
The following events are AESIs and must be reported to the sponsor expeditiously:

- Ventricular arrhythmias (e.g., ventricular extrasystoles, ventricular tachycardia, ventricular arrhythmia, ventricular fibrillation)

For study treatment containing biologic products:

- Suspected transmission of an infectious agent by the study intervention whereby any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings indicating an infection in a participant exposed to a medicinal product. This term applies ONLY when a contamination of the study intervention is suspected, NOT for infections supported by the mode of action such as immunosuppression.

PI Responsibilities



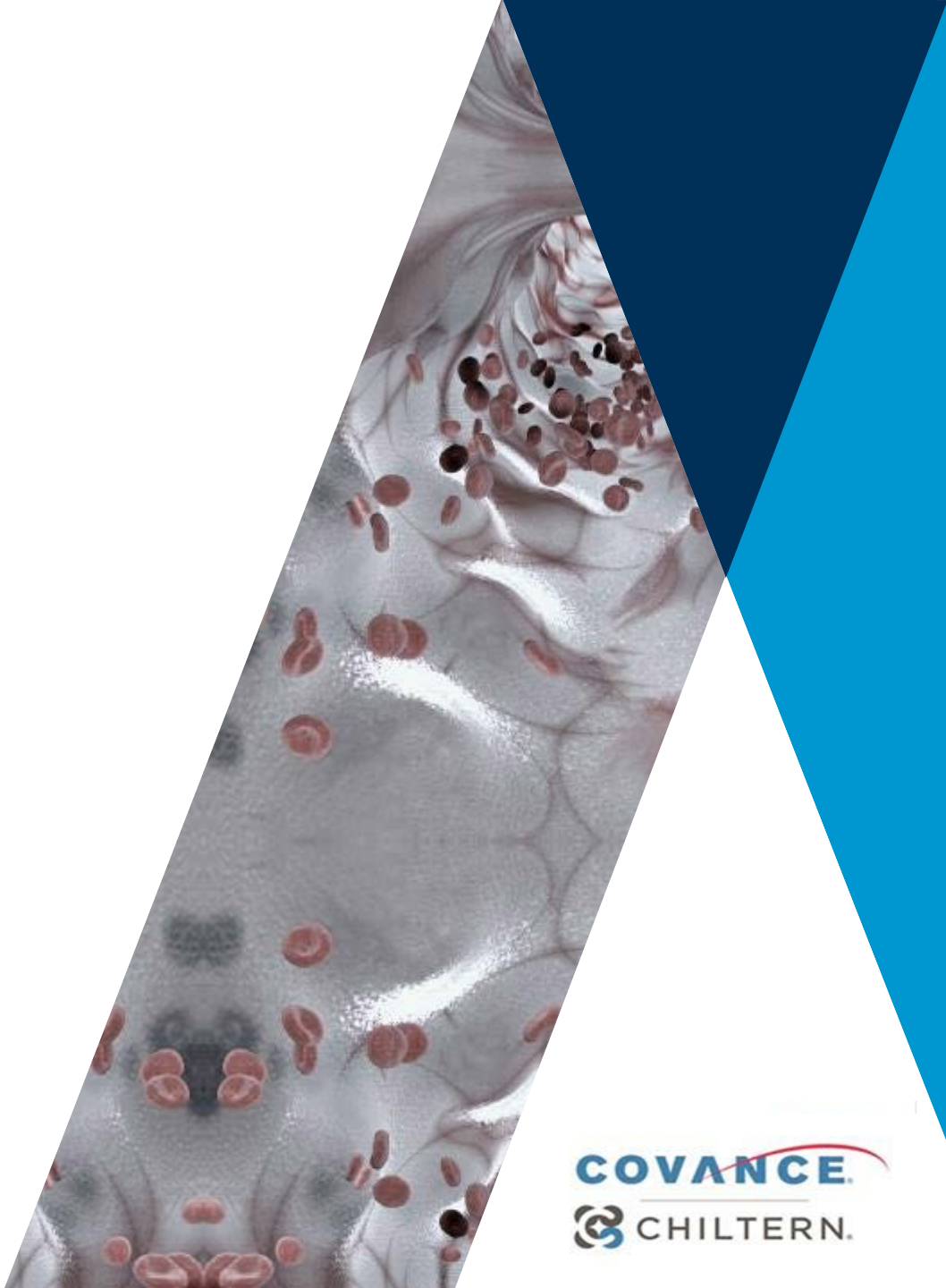
Investigator Obligations

- ✓ Protecting the rights, safety, and welfare of trial subjects
- ✓ Providing medical care for trial subjects
- ✓ Informing any trial subject, or any persons used as controls, that the investigational product(s) being used are for investigational purposes
- ✓ Ensuring that informed consent is obtained from all trial subjects prior to any study-related procedures being performed
- ✓ Ensuring that all trial staff are qualified by education, training, and experience to ensure proper conduct of the trial
- ✓ Utilizing a compliant IRB and maintaining communication
- ✓ Ensuring IRB approval and re-approval is obtained
- ✓ Promptly reporting all changes in research activity/progress to the IRB
- ✓ Ensuring that no changes to the protocol or conduct of the study occur without IRB approval except when necessary to eliminate apparent immediate hazards to human subjects
- ✓ Agreeing to conduct the study in accordance with the IRB-approved protocol, investigator agreement, and applicable regulations

Investigator Obligations

- ✓ Documenting all deviations from the protocol
- ✓ Personally conducting or supervising the investigation
- ✓ Obtaining written Sponsor approval prior to publishing any information obtained in this study
- ✓ Agreeing to report to the Sponsor AEs that occur in the course of the investigation (21 CFR 312.64)
- ✓ Immediately notifying the Sponsor and Monitor of any SAEs
- ✓ Notifying the Sponsor/Covance immediately if notified of an inspection by the FDA
- ✓ Maintaining control of study drugs and accountability
- ✓ Agreeing to maintain adequate and accurate records, make those records available for inspection, and retain records according to 21 CFR 312.62 and 312.68
- ✓ Agreeing to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312 and GCP Guideline

Site Tour



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Site Tour - Equipment

- ✓ Centrifuge (Refrigerated for PK processing?)
- ✓ Laboratory/Sample Storage (Freezer?)
- ✓ Dry Ice Accessibility
- ✓ Crash cart/ process for emergencies
- ✓ Vital Signs Equipment
  - Blood Pressure Machine(s)
  - Pulse Oximeter
  - Scale – Height & Weight
  - Thermometer

Study Supplies / Equipment / Facilities

- ✓ Record Storage
- ✓ EMR (if applicable)
- ✓ Back-up Power Supply
- ✓ EDC/Internet Capabilities
- ✓ Calibration Requirements/Checks
- ✓ Pharmacy/IP Storage
- ✓ Subject exam rooms
- ✓ ECG, ECHO/MUGA scan
- ✓ PET-CT/CT/MRI

Site Evaluation

Investigator Profile & Experience

Nurses/Study Coordinators/Other Staff

Patient Population

- Competing Studies
- Site & Patient Interest
- Recruitment Strategies
  - Practice
  - Referrals
  - Other

Regulatory & Related Topics

Thank you!

- **QUESTIONS?**