PROTOCOL

TITLE:	A Phase 1/2 Proof-of-Concept Study of the Combination of Acalabrutinib and Vistusertib in Subjects with Relapsed/Refractory B-Cell Malignancies
PROTOCOL NUMBER:	ACE-LY-110
STUDY DRUGS:	Acalabrutinib (ACP-196) and vistusertib (AZD2014)
IND NUMBER:	133812
EUDRACT NUMBER:	2016-003736-21
SPONSOR MEDICAL MONITOR:	PPD
SPONSOR:	Acerta Pharma BV Kloosterstraat 9 5349 AB Oss The Netherlands
ORIGINAL PROTOCOL:	Version 0.0 – 02 February 2017
AMENDMENT 1:	Version 1.0 – 26 March 2017
AMENDMENT 2:	Version 2.0 – 06 February 2018
AMENDMENT 3:	*Version 3.0 – 29 March 2019*

Confidentiality Statement

PROTOCOL APPROVAL PAGE

I have carefully read Protocol ACE-LY-110 entitled “A Phase 1/2 Proof-of-Concept Study of the Combination of Acalabrutinib and Vistusertib in Subjects with Relapsed/Refractory B-cell Malignancies”. I agree to conduct this study as outlined herein and in compliance with Good Clinical Practices (GCP) and all applicable regulatory requirements. Furthermore, I understand that the sponsor, Acerta Pharma, and the IRB/IEC must approve any changes to the protocol in writing before implementation.

I agree not to divulge to anyone, either during or after the termination of the study, any confidential information acquired regarding the investigational product and processes or methods of Acerta Pharma. All data pertaining to this study will be provided to Acerta Pharma. The policy of Acerta Pharma requires that any presentation or publication of study data by clinical investigators be reviewed by Acerta Pharma, before release, as specified in the protocol.

Principal Investigator’s Signature Date

Print Name

SUMMARY OF AMENDMENT 3

The primary reason for amending the study protocol is to provide information about the closure of the study before initiation of Part 2 and to allow subjects who are deriving clinical benefit to remain on study treatment. On 21 May 2018, a decision was made by the sponsor to stop enrollment and close this study after evaluating the safety, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of acalabrutinib in combination with vistusertib at Dose Level -1 and Dose Level 0. In general, the acalabrutinib and vistusertib (an mTOR1 and mTOR2 dual inhibitor) combination was well tolerated in subjects with relapsed/refractory diffuse large B-cell lymphoma enrolled in Dose Level -1 and Dose Level 0. However, modest clinical efficacy was observed at both dose levels. CCI [redacted] PK modeling indicated that increasing dose levels and/or changing dosing schedules would not improve target engagement. A total of 25 subjects have enrolled in the study; 23 subjects have been treated and are no longer participating in the study. The protocol is being amended to allow 2 subjects who are still receiving study treatment and deriving clinical benefit to remain on study treatment beyond the first 12 cycles and until disease progression.

The schedule of the computed tomography scans was changed from occurring every 8 weeks to every 12 weeks. The frequency of follow-up visits was changed from every 4 weeks to every 12 weeks. Updates were made to the appendix that provides investigators with information to identify and report cases of severe liver toxicity (Potential Hy's law and Hy's law cases), for consistency across the sponsor's clinical development program. Changes have been made to the inclusion criteria, reproductive toxicity section, and pregnancy section to align with the Clinical Trial Facilitation Group recommendations related to contraception and pregnancy testing in clinical studies and for consistency across the sponsor's clinical development program.

Minor clarification edits and typographical corrections have been made throughout the protocol and are not highlighted below. The following substantive changes or edits were made as part of this amendment:

Change	Rationale
Synopsis Updated to reflect changes made throughout the protocol.	To ensure consistency between the body of the protocol and the synopsis
Section 1.1 Acalabrutinib (ACP-196) Revised text as shown (**bold** indicates new text): Acalabrutinib (CALQUENCE®) ~~was recently~~**has been** approved in the United States **and other markets** for the treatment of **adult** patients with MCL who have ~~had~~**received** at least 1 prior therapy (CALQUENCE package insert).	To provide updated information about acalabrutinib approvals
Section 3.0 STUDY DESIGN Revised text as shown (**bold** indicates new text): This study is a multicenter, open-label, randomized (Part 1 only) parallel group study to be conducted at approximately 15 to 20 sites. The study ~~is~~**was originally designed to be** divided into 2 parts. The Phase 1 portion of the study (Part 1) evaluate~~s~~*d* the safety, PK, and PD of combining acalabrutinib 100 mg twice a day (bid) and vistusertib (various doses and schedules). Part 1 ~~will~~**was to** be used to select the vistusertib dose and schedule for Phase 2. The Phase 2 portion of the study (Part 2) ~~allows~~**was to allow** for expansion groups in select B-cell histologies to further evaluate safety, efficacy, and PKPD of the combination treatment**; however, the sponsor has decided to close the study prior to initiating Part 2**. **…** Part 1 will enroll approximately 12 to 36 subjects depending on safety. The safety results (eg, DLTs, discontinuation due to adverse events and tolerability) of Part 1 ~~will~~**were to** be used to select the vistusertib dose/schedule for Part 2. Any DLTs attributed to the combination after cycle 1 ~~will~~**were** also **to** be taken into consideration when determining the vistusertib dose and schedule for Part 2. ~~Enrollment into Part 2 will proceed if a dose and schedule has been successfully selected for vistusertib from Part 1.~~ **Enrollment into Dose Level 1 and beyond (Part 2) was discontinued by the sponsor. The primary reason for discontinuation of Part 2 was that inhibition of the Torc-2 protein, which is a target of vistusertib, was not adequate as determined by PD studies. In addition, PK data from subjects at vistusertib Dose Level 0 suggested that increasing the dose to Level 1 would only increase exposure by approximately 20%, which is not expected to provide sufficient Torc-2 coverage to differentiate from approved Torc-1 inhibitors and could increase risk for toxicity.** **Part 2** Part 2 **was designed to consist~~s~~** of expansion groups of 15 or 20 subjects per histology (N≤35 total for Part 2) provided the safety results from Part 1 of the study indicate**d** that further evaluation of the combination ~~is~~**was** warranted. **As mentioned above, the study was**	To reflect the decision made by the sponsor to stop enrollment and close the study after evaluating the safety, efficacy, PK, and PD of acalabrutinib in combination with vistusertib at Dose Level -1 and Dose Level 0

Change	Rationale
closed before initiating Part 2. ~~The possible expansion groups for Part 2 may include adult subjects with the following relapsed/refractory disease types:~~ ~~• De novo non-GCB DLBCL (n≤20)~~ ~~• De novo GCB DLBCL (n≤15)~~ ~~Treatment with acalabrutinib and vistusertib, in Part 1 and Part 2, may be continued until disease progression or an unacceptable drug-related toxicity occurs as defined in the protocol. Subjects who do not tolerate vistusertib may continue to receive acalabrutinib monotherapy provided they are deriving clinical benefit. Dose modification provisions are provided in Section 3.8. All subjects who discontinue study treatment (ie, both drugs) will have an SFU visit 30 (+ 7) days after the last dose of study drug(s). In addition, any subjects who discontinue study treatment (ie, both drugs) before documentation of disease progression will be followed according to standard of care to collect information on when documented disease progression occurs and whether a new anticancer therapy is started. All subjects will be followed for survival.~~ Subjects showing clinical benefit (ie, no disease progression) and who are tolerating study treatment may remain on study for up to a total of 12 cycles of treatment. Subjects who have received 12 cycles of treatment (ie, been on study for approximately 12 months) and are deriving clinical benefit from acalabrutinib monotherapy or the combination of acalabrutinib and vistusertib may **remain on study treatment beyond the first 12 months until disease progression occurs or** be eligible to enroll in either a rollover study of acalabrutinib monotherapy or a rollover study of the combination of acalabrutinib and vistusertib, respectively. **…**	Revised to allow subjects who are deriving clinical benefit from study treatment to remain on study treatment beyond the first 12 months of treatment
Figure 2. Study Schema The following footnote was added to Figure 2: **Note: On 21 May 2018, a decision was made by the sponsor to stop enrollment and close the study before initiating Dose Level 1 and Part 2.**	Study schema was revised to include a footnote clarifying the revision to the study design.
Section 3.1.1 Safety Parameters Revised text as shown (**bold** indicates new text): For consistency of interpretation, AEs and laboratory results will be coded using MedDRA, and the severity of AEs will be graded using the CTCAE, Version ~~4.03~~**5.0** or higher.	Updated Common Terminology Criteria for Adverse Events (CTCAE) version number

Change	Rationale
Section 3.1.2 Pharmacodynamic, Pharmacokinetic, and Biomarker Parameters Revised text as shown (**bold** indicates new text): The following PK parameters will be calculated, whenever possible, from plasma concentrations of acalabrutinib and vistusertib **(Note: These will not be collected or assessed for subjects whose study participation extends past the first 12 cycles.)**: • $AUC_{0\text{-last}}$: Area under the plasma concentration-time curve calculated using linear trapezoidal summation from time 0 to time last, where "last" is the time of the last measurable concentration • $AUC_{0\text{-inf}}$: Area under the plasma concentration-time curve from 0 to infinity, calculated using the formula: $AUC_{0\text{-inf}}=AUC_{0\text{-last}} + C_{last} / \lambda_z$, where λ_z is the apparent terminal elimination rate constant (whenever possible) • C_{max}: Maximum observed plasma concentration • T_{max}: Time of the maximum plasma concentration (obtained without interpolation) • $t_{½}$: Terminal elimination half-life • λ_z: Terminal elimination rate constant • CL/F: Oral clearance • V_z/F: Oral volume of distribution	Revised to note that PK, PD, and biomarker parameters would not be assessed for the subjects who continue study treatment beyond 12 cycles
Section 3.1.3 Efficacy Parameters Revised text as shown (**bold** indicates new text): Analysis of efficacy parameters is provided in Section 5.5.4. **The efficacy evaluations will not be assessed for subjects whose study participation extends past the first 12 cycles.**	Efficacy will not be assessed for the subjects who continue study treatment beyond 12 cycles.
Section 3.2.1 Rationale for Combining mTOR and BTK Inhibition Revised text as shown (**bold** indicates new text): As is typical of dose-finding studies, … Therefore, the purpose of Part 2 ~~is~~**was** to evaluate the combination therapy in both subtypes to determine whether the combination therapy is active across subtypes or shows preferential activity for a particular subtype. **On 21 May 2018, a decision was made by the sponsor to stop enrollment and close this study after evaluating the safety, efficacy, PK, and PD of acalabrutinib in combination with vistusertib at Dose Level -1 and Dose Level 0. In general, the acalabrutinib and vistusertib (an mTOR1 and mTOR2 dual inhibitor) combination was well tolerated in subjects with relapsed/refractory DLBCL enrolled in Dose Level -1 and Dose Level 0. However, modest clinical efficacy was observed at both dose levels.** CCI [redacted] **PK modeling indicated that increasing dose levels and/or changing dosing schedules would not improve target engagement.** ~~Information from this study will be used to guide the design of future studies with the combination.~~	Revisions made to reflect the decision made by the sponsor to stop enrollment and close the study after evaluating the safety, efficacy, PK, and PD of acalabrutinib in combination with vistusertib at Dose Level -1 and Dose Level 0.

Change	Rationale
Section 3.2.2 Dose Selection Rationale Revised text as shown (**bold** indicates new text): Vistusertib has been evaluated at several doses and schedules. Monotherapy vistusertib 50 mg bid continuous and 125 mg bid 2 days on and 5 days off has been well tolerated. However, to reduce the potential for overlapping toxicities, the vistusertib dosages being evaluated have been reduced to 35 mg bid continuous (Level -1 for continuous dosing schedule) and 100 mg bid 2 days on and 5 days off (Level -1 for intermittent dosing schedule). ~~Amendment 2 of this protocol adds higher levels (Level +1) for vistusertib in Part 1 should the target level(s) be well tolerated with acalabrutinib. As the target levels were derived from experience of vistusertib in subjects with solid tumors, the higher levels of vistusertib may be more efficacious in subjects with lymphoma and, therefore, warrant evaluating for potential toxicity. The proposed higher dose levels for vistusertib are within the range of doses previously evaluated in subjects with solid tumors (refer to the Investigator Brochure for detailed information). As described previously, this study incorporates a formal DLT review to select the most tolerated vistusertib dosage/schedule for the expansion portion of the study.~~ **Amendment 2 of this protocol added a higher dose level of vistusertib (Level +1) to Part 1 of the protocol. However, as mentioned previously, the sponsor stopped the study after evaluating the efficacy, safety, PD, and PK data from the subjects treated with the lower dose levels of vistusertib.**	Revisions made to reflect the decision made by the sponsor to stop enrollment and close the study after evaluating the safety, efficacy, PK, and PD of acalabrutinib in combination with vistusertib at Dose Level -1 and Dose Level 0.
Section 3.3.1 Inclusion Criteria Revised text as shown (**bold** indicates new text): Inclusion criterion #12 was modified as follows: 12. Men ~~should be willing to~~**who are sexually active must** use barrier contraception (ie, condoms) **in addition to the highly effective contraception** and refrain from sperm donation during the study and ~~for a washout period of 120~~ **until 2**-days after ~~discontinuing study drug(s)~~**the subject's last dose of acalabrutinib or 16 weeks after the subject's last dose of vistusertib, whichever is longer.** If not done previously, storage of sperm before receiving vistusertib will be advised to male subjects with a desire to have children.	Revised to align with current acalabrutinib and vistusertib contraception information
Section 3.3.2 Exclusion Criteria Revised text as shown (**bold** indicates new text): Exclusion criterion #15 was modified as follows: 15. Unresolved toxicities from prior anticancer therapy, defined as having not resolved to CTCAE, Version ~~4.03~~**5.0** Grade 0 or 1, or to the levels dictated in the inclusion/exclusion criteria, with the exception of alopecia.	Updated CTCAE version number

<table>
<tr><th>Change</th><th>Rationale</th></tr>
<tr><td>

Section 3.5 Study Treatment Schedule

Revised text as shown:

<table>
<tr><th colspan="5">Vistusertib Dose Levels and Schedules</th></tr>
<tr><th></th><th>Dose Level</th><th>Schedule Type</th><th>Dose Schedule</th><th>Weekly Dose</th></tr>
<tr><td rowspan="3">SCHEDULE 1</td><td>Starting dose (Level -1)</td><td>Continuous</td><td>35 mg twice daily continuous</td><td>490 mg</td></tr>
<tr><td>Target dose (Level 0)</td><td>Continuous</td><td>50 mg twice daily continuous</td><td>700 mg</td></tr>
<tr><td>~~Level +1 dose~~</td><td>~~Continuous~~</td><td>~~75 mg twice daily continuous~~</td><td>~~1050 mg~~</td></tr>
<tr><td rowspan="4">SCHEDULE 2</td><td>Level -2 dose</td><td>Intermittent</td><td>75 mg twice daily 2 days on/5 days off</td><td>300 mg</td></tr>
<tr><td>Starting dose (Level -1)</td><td>Intermittent</td><td>100 mg twice daily 2 days on/5 days off</td><td>400 mg</td></tr>
<tr><td>Target dose (Level 0)</td><td>Intermittent</td><td>125 mg twice daily 2 days on/5 days off</td><td>500 mg</td></tr>
<tr><td>~~Level +1 dose~~</td><td>~~Intermittent~~</td><td>~~150 mg twice daily 2 days on/5 days off~~</td><td>~~600 mg~~</td></tr>
</table>

</td><td>Revised to remove the dose-level information for the discontinued Level +1 dose</td></tr>
<tr><td>

Section 3.6 Duration of Therapy

Revised text as shown (**bold** indicates new text):

Treatment with acalabrutinib and vistusertib, in Part 1~~ and Part 2~~, may be continued until disease progression or an unacceptable drug-related toxicity occurs as defined in the protocol. Subjects who do not tolerate vistusertib may continue to receive acalabrutinib monotherapy provided they are deriving clinical benefit.

Subjects showing clinical benefit and who are tolerating study treatment may remain on study for up to 12 cycles of treatment. Subjects who have received 12 cycles of treatment (ie, been on study for approximately 12 months) and are deriving clinical benefit from acalabrutinib monotherapy or the combination of acalabrutinib and vistusertib may **remain on study treatment beyond the first 12 months until disease progression occurs or** be eligible to enroll in either a rollover study of acalabrutinib monotherapy or a rollover study of the combination of acalabrutinib and vistusertib, respectively.

</td><td>Revised to allow subjects who are deriving clinical benefit from study treatment to remain on study treatment beyond the first 12 months of treatment</td></tr>
</table>

<table>
<tr><th>Change</th><th>Rationale</th></tr>
<tr><td>

Section 3.8 Dosing Delays and Modifications

Starting dose of 150 mg vistusertib deleted from dose reduction table.

Table 5 Vistusertib dose reduction options

Starting dose	1st dose reduction	2nd dose reduction	3rd dos reductic
35 mg	25 mg	discontinue	not applic
50 mg	35 mg	25 mg	discontir
75 mg	50 mg	25 mg	discontir
100 mg	75 mg	50 mg	25 mg
125 mg	100 mg	75 mg	50 mg
~~150 mg~~	~~125 mg~~	~~100 mg~~	~~75 mg~~

a If allowed after consultation with medical monitor

</td><td>Revised to remove the dose-level information for the discontinued dose</td></tr>
<tr><td>

Section 3.11.7 Reproductive Toxicity

Revised text as shown (**bold** indicates new text):

Definition of contraception:
~~(1) Practice abstinence† from heterosexual intercourse;~~
~~OR~~
~~(2) Use (or have their partner use) highly effective contraception during heterosexual intercourse.~~
~~Highly effective methods of contraception are‡:~~
~~Combination method: Use of a male condom is required and one of the following:~~

- ~~Use of medroxyprogesterone acetate depot injection (Depo-Provera™). (Please note: use of any other oral, injected, or implanted hormonal methods of contraception cannot be considered highly effective as it is currently unknown whether vistusertib may reduce their effectiveness.)~~
- ~~Vasectomized partner (condom use in male subjects is recommended to prevent possible direct exposure in case of a pregnant female partner)~~
- ~~Diaphragm with spermicide~~
- ~~Cervical cap with spermicide (nulliparous women only)~~
- ~~Contraceptive sponge (nulliparous women only)~~
- ~~Intrauterine device (IUD)~~
- ~~Bilateral tubal ligation~~

~~†Abstinence (relative to heterosexual activity) can only be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and IECs/IRBs. Periodic abstinence (eg, calendar, ovulation, sympto-thermal, and post-ovulation methods) and withdrawal are not acceptable methods of contraception.~~

~~‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.~~

</td><td>Revised to correct the definition of *highly effective* contraception to align with the Clinical Trial Facilitation Group guidance</td></tr>
</table>

Change	Rationale
Highly effective methods of contraception (to be used during heterosexual activity) are defined as methods that can achieve a failure rate of <1% per year when used consistently and correctly. Such methods include the following: • **Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, which may be oral, intravaginal, or transdermal** • **Progestogen-only hormonal contraception associated with inhibition of ovulation, which may be oral, injectable, or implantable** • **Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)** • **Bilateral tubal occlusion** • **Vasectomy of a female subject's male partner (with medical assessment and confirmation of vasectomy surgical success)** • **Sexual abstinence (only if refraining from heterosexual intercourse during the entire period of risk associated with the study treatments)** **Hormonal contraception may be susceptible to interaction with study or other drugs, which may reduce the efficacy of the contraception method.** **Abstinence (relative to heterosexual activity) can only be used as the sole method of contraception if it is consistently employed during the entire period of risk associated with the study treatments as the subject's preferred and usual lifestyle. Periodic abstinence (eg, calendar, ovulation, sympto-thermal, and post-ovulation methods) and withdrawal are not acceptable methods of contraception.** **If a contraceptive method is restricted by local regulations/guidelines, then it does not qualify as an acceptable highly effective method of contraception for subjects participating at sites in the relevant country/region.** … Men **who have a partner who is a woman**~~should be asked to avoid unprotected sex (ie, always use a condom) with women~~ of childbearing potential **must use highly effective contraception with the additional use of a condom** during the study and for ~~a washout period of 120 days after discontinuing study drug(s)~~**16 weeks after the subject's last dose of vistusertib.** Male subjects should refrain from donating sperm from the start of dosing until ~~120 days~~**16 weeks** after ~~discontinuing~~ the ~~study drug(s)~~ **subject's last dose of vistusertib.** If male subjects wish to father children, they should be advised to arrange for freezing of sperm samples before receiving the first dose of ~~study drug(s)~~**vistusertib.** Subjects should promptly notify the investigator if they or their partners become pregnant during this study or within ~~120~~**2** days after their last dose of ~~study drug(s)~~**acalabrutinib or 16 weeks after the subject's last dose of vistusertib, whichever is longer.** If a woman becomes pregnant during the treatment period, she must discontinue acalabrutinib and vistusertib. Pregnancy must be reported as outlined in Section 6.2.3.	Revised to align with current acalabrutinib and vistusertib contraception information

Change	Rationale
Section 4.1.22 Pharmacokinetics Revised text as shown: Vistusertib PK blood sampling (2 mL per sample) will be collected at predose and at approximately 1, 2, 4, and 6 hours postdose on Cycle 1 Day 1 and Cycle 1 Day 22 for all subjects in Part 1~~ and approximately 9 selected subjects in Part 2. The same 9 subjects from Part 2 will have samples collected for acalabrutinib PK as described below~~. Acalabrutinib PK blood sampling (2 mL per sample) will be collected. For Part 1, samples will be collected from all subjects on Cycle 1 Day 1 and Cycle 1 Day 22 predose and at approximately 1, 2, 4 and 6 hours postdose.~~For Part 2, 9 selected subjects will have acalabrutinib PK samples taken on Cycle 0 Day -1 and Cycle 1 Day 22 predose and approximately 1, 2, 4 and 6 hours postdose.~~	Revised to reflect the decision made by the sponsor to stop enrollment and close the study before proceeding to Part 2
Section 4.1.25 Pharmacodynamic Samples Revised text as shown: CCI [redacted]	Revised to reflect the decision made by the sponsor to stop enrollment and close the study before proceeding to Part 2
Section 4.1.27 ~~Whole Blood Immunophenotyping~~ Section has been deleted ~~**Whole blood immunophenotyping will be done in Part 2 of the study only.** Whole blood samples (a 4-mL and 5-mL sample for 9 mL total of whole blood) will be collected for flow cytometry-based immunophenotyping. Samples will be collected at screening and predose on Cycle 1 Day 1, Cycle 1 Day 15 and Cycle 2 Day 1. Populations monitored may include, but are not limited to, leukocyte or lymphocyte subsets (eg, T, B and NK cells) and their respective activation states. The results of this exploratory research will be reported separately and will not form part of the CSR. Refer to the laboratory manual for instructions on collection and shipment of the whole blood immunophenotyping samples. All testing will be done by the sponsor or designee.~~	Revised to reflect the decision made by the sponsor to stop enrollment and close the study before proceeding to Part 2
Section 4.1.30 Tumor Assessments Revised text as shown (**bold** indicates new text): **For all histologies:** Baseline tumor assessments will be performed using radiologic imaging by CT with contrast and PET-CT covering neck, chest, abdomen, and pelvis within 30 days before the first dose of study drug. Radiologic scans (ie, contrast CT) will be repeated every ~~2~~**3** cycles (ie, approximately every ~~8~~**12** weeks ± 7 days). PET-CT also will be repeated on the same schedule, when required, per Section 4.3 of the protocol. For subjects with baseline hepatosplenomegaly, the cranial-caudal measurement of the spleen and longest diameter of the liver will be assessed at screening and subsequent response evaluations.	Revised to extend the CT scans to every 3 cycles for the subjects who remain on study treatment beyond 12 cycles

Section 5.2 Rationale for Sample Size Revised text as shown (**bold** indicates new text): ~~Depending on dose escalation/de-escalation and enrollment in the expansion groups up to 71 subjects will be enrolled in this study.~~ In Part 1 (dose selection), enrollment of 6 subjects per dose level limits the number of subjects exposed consistent with the expected safety profiles of the study drugs, but includes sufficient subjects to explore effects on PD biomarkers of BTK and mTOR inhibition. The trial employ~~s~~**ed** the standard NCI definition of MTD (dose associated with DLT in <33.3% of subjects assessed during cycle 1). A maximum of 3 dose levels ~~will be~~**were to have been** explored in each of the two schedules (continuous/intermittent vistusertib dosing). The maximum number of subjects in Part 1 ~~is~~**was** therefore 36. **The sponsor stopped the study in Part 1 after treating 25 subjects with the first 2 dose levels of vistusertib.** ~~The recommended vistusertib dose and schedule from Part 1 will be evaluated further in two cohorts in Part 2: a de novo non-GCB cohort with target sample size 20, and a de novo GCB cohort with target sample size 15. Wherever possible, subjects with the same subtype of DLBCL, who have received the recommended dose/schedule of vistusertib in Part 1, will be pooled for analysis. Note: Local DLBCL subgroup classifications will be centrally confirmed for analysis purposes (details provided in the Statistical Analysis Plan). The total number of subjects enrolled into Part 2 will be up to 35. This sample size is large enough to evaluate further the safety and PKPD of the chosen dose/schedule for vistusertib from Part 1, and gives a reasonable chance of detecting an efficacy signal, should one exist.~~ ~~The primary analysis will be conducted after all ongoing subjects have had the opportunity to complete at least 3 scheduled post-baseline scans. No formal statistical testing will be performed. Confidence intervals will be constructed around the objective response rate observed, and this will enable decisions to be made around the likely success of future studies. Historical response rates in relapsed/refractory DLBCL are in the region of 30% to 55%, with some evidence that response rates are higher for the non-GCB subtype (Hernandez-Ilizaliturri et al 2011; Morschhauser et al 2014; Van Den Neste et al 2016a; Van Den Neste et al 2016b; Wilson et al 2015; Witzig et al 2011). The following examples give an indication of the level of precision that will be achieved in this study:~~ ~~In the non-GCB subgroup~~ • ~~If the observed response rate is 35% (7/20), the 2-sided 80% confidence interval will be (21%, 52%).~~ • ~~If the observed response rate is 60% (12/20), the 2-sided 80% confidence interval will be (43%, 75%).~~ ~~In the GCB subgroup~~ • ~~If the observed response rate is 20% (3/15), the 2-sided 80% confidence interval will be (8%, 39%).~~ • ~~If the observed response rate is 33% (5/15), the 2-sided 80% confidence interval will be (17%, 53%).~~ ~~In addition to ORR, the criteria for success will take into account the observed safety and tolerability data, and the other efficacy endpoints, in particular the DRR.~~ ~~Subjects will continue to be followed for survival after objective disease progression. A final analysis will be performed after the earlier of 12~~	Revised to reflect the decision made by the sponsor to stop enrollment and close the study before proceeding to Part 2

Change	Rationale
~~months after the last subject is recruited to Part 2 or when 50% of the subjects in Part 2 have died due to any cause.~~ ~~**Interim analysis**~~ CCI [redacted]	
Section 5.5.1 Safety Revised text as shown (**bold** indicates new text): Verbatim descriptions of AEs will be mapped according to the MedDRA thesaurus terms and graded according to NCI CTCAE, v~~4.03~~**5.0** or higher.	Updated CTCAE version number
Section 5.5.5 Pharmacokinetic Analyses Revised text as shown (bold indicates new text): The plasma PK of acalabrutinib and vistusertib will be characterized using noncompartmental analysis. The following PK parameters will be calculated, whenever possible, from plasma concentrations of analytes **(Note: These will not be collected or assessed for subjects whose study participation extends past the first 12 cycles.)**: • $AUC_{0\text{-last}}$: Area under the plasma concentration-time curve calculated using linear trapezoidal summation from time 0 to time last, where "last" is the time of the last measurable concentration • $AUC_{0\text{-inf}}$: Area under the plasma concentration-time curve from 0 to infinity, calculated using the formula: $AUC_{0\text{-inf}} = AUC_{0\text{-last}} + C_{last} / \lambda_z$, where λ_z is the apparent terminal elimination rate constant • C_{max}: Maximum observed plasma concentration • T_{max}: Time of the maximum plasma concentration (obtained without interpolation) • $t_{½}$: Terminal elimination half-life (whenever possible) • λ_z: Terminal elimination rate constant (whenever possible) • CL/F: Oral clearance • V_z/F: Oral volume of distribution	Revised to note that PK parameters would not be assessed for the subjects who continue study treatment beyond 12 cycles

Change	Rationale
Section 6.1.3 Severity Revised text as shown (**bold** indicates new text): Definitions found in the CTCAE version ~~4.03~~**5.0** or higher will be used for grading the severity (intensity) of AEs. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE.	Updated CTCAE version number
Section 6.2.3 Pregnancy Revised text as shown (**bold** indicates new text): Any uncomplicated pregnancy that occurs during this study will be reported. All pregnancies that are identified during or after this study, wherein the estimated date of conception is determined to have occurred from the time of consent to ~~120~~**2** days after the last dose of ~~study drug(s)~~ **acalabrutinib or 16 weeks after the last dose of vistusertib, whichever is longer,** will be reported, followed to conclusion, and the outcome reported, as long as the subject or subject's partner is willing to participate in follow up. Upon completion of the pregnancy, additional information on the mother, pregnancy, and baby will be collected and sent to CCI .	Revised to align with current acalabrutinib and vistusertib pregnancy information
Appendix 1 Schedule of Assessments (Acalabrutinib + Vistusertib) The Schedule of Assessments was revised to remove Part 2 assessments and long-term follow up and to add an assessment column for extended study treatment (ie, for subjects continuing study participation >12 cycles). The frequency of the CT scan was also revised to occur every 3 cycles instead of every 2 cycles.	Revised to reflect changes in the protocol
Appendix 2 Schedule of Assessments (Acalabrutinib Monotherapy) The Schedule of Assessments was revised to remove long-term follow up and to add an assessment column for extended study treatment (ie, for subjects continuing study participation >12 cycles).	Revised to reflect changes in the protocol
Appendix 5 Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law Revised text in this appendix	Revised to reflect standard practice concerning Hy's law across the sponsor's clinical development program

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ABBREVIATIONS

Abbreviation or special term	Explanation
λ_z	Terminal elimination rate constant
4EBP1	Eukaryotic translation initiation factor 4E (eIF4E)-binding protein 1
5PS	5-point scale
ABC	Activated B cell-like subtype of diffuse large B-cell lymphoma
AE	Adverse event
ACP-196	Acalabrutinib
AKT	Protein kinase B
ALC	Absolute lymphocyte count
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
AMPK, AMP	Activated protein kinase
ANC	Absolute neutrophil count
anti-HBc	Hepatitis B core antibody
anti-HBs	Hepatitis B surface antibody
aPTT	Activated partial thromboplastin time
ASCT	Autologous stem cell transplant
AST	Aspartate aminotransferase
$AUC_{0\text{-inf}}$	Area under the plasma concentration-time curve from 0 to infinity, calculated using the formula: $AUC_{0\text{-inf}} = AUC_{0\text{-last}} + C_{last} / \lambda_z$, where λ_z is the apparent terminal elimination rate constant
$AUC_{0\text{-last}}$	Area under the plasma concentration-time curve calculated using linear trapezoidal summation from time 0 to time last, where “last” is the time of the last measurable concentration

Abbreviation or special term	Explanation
AZD2014	Vistusertib
BAD Bcl-2	Associated death promoter
B-ALL	Burkitt acute lymphoblastic leukemia
BCR	B-cell receptor
BCRP	Breast cancer resistance protein
bid/BID	Twice per day
BTK	Bruton tyrosine kinase
BUN	Blood urea nitrogen
C	Cycle
CBC	Complete blood count
cGMP	Current Good Manufacturing Practices
CIRS-G	Cumulative Illness Rating Scale-Geriatric
CIs	Confidence intervals
CL/F	Oral clearance
CLL	Chronic lymphocytic leukemia
C_{max}	Maximum observed plasma concentration
CMV	Cytomegalovirus
CNS	Central nervous system
CR	Complete remission/response
CFR	Code of Federal Regulations
CSR	Clinical Study Report
CT	Computed tomography

Abbreviation or special term	Explanation
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
CYP	Cytochrome P450
Cys	Cysteine
d or D	Day(s)
DFU	Discontinuation follow-up;
DILI	Drug induced liver injury
DLBCL	Diffuse large B-cell lymphoma
DLCO	Carbon monoxide diffusing capacity
DLT/DLTs	Dose-limiting toxicities
DOR	Duration of response
DRR	Durable response rate
ECG/ECGs	Electrocardiogram(s)
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group;
eCRF	Electronic case report form
EDC	Electronic data capture
Enrolled subject	An enrolled subject is a subject who has signed informed consent and has received at least 1 dose of study drug(s)
ESCR	Externally sponsored collaborative research
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FL	Follicular lymphoma

Abbreviation or special term	Explanation
FOXO	Forkhead box protein O1
FSH	Follicle-stimulating hormone
GCB	Germinal center B-cell subtype of diffuse large B-cell lymphoma
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GI	Gastrointestinal
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GSK3	Glycogen synthase kinase 3
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C Virus
HIV	Human immunodeficiency Virus
HL	Hy's law
ICF	Informed Consent Form
Ig	Immunoglobulin
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
INR	International normalization ratio
Interm.	Intermittent dosing
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IUD	Intrauterine device
IVIG	Intravenous immunoglobulins
IXRS	Interactive Voice/Web Response System

Abbreviation or special term	Explanation
JC (virus)	John Cunningham virus
KM	Kaplan-Meier
LDH	Lactate dehydrogenase
LDi	Longest transverse diameter of a lesion
LH	Luteinizing hormone
LTF	Long-term follow-up
LV	Left ventricular
LVEF	Left ventricular ejection fraction
MCL	Mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
mos	Months
MRI	Magnetic resonance imaging
MTD/MTDs	Maximum tolerated dose(s)
mTOR	Mammalian target of rapamycin
MUGA	Multigated acquisition
MZL	Marginal zone lymphoma
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NK	Natural killer
Non-GCB	Non-germinal center B-cell subtype of diffuse large B-cell lymphoma
NYHA	New York Heart Association
ORR	Overall response rate

Abbreviation or special term	Explanation
OS	Overall survival
PBMCs	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PDK1	Phosphoinositide-dependent protein kinase 1
PE	Physical exam
PET	Positron-emission tomography
PFS	Progression-free survival
P-gp	Permeability glycoprotein
PHL	Potential Hy's law
PHLPP	PH domain and leucine rich repeat protein phosphatases
PI3K	Phosphoinositide 3 kinase
PIP	Phosphatidylinositol phosphate
PK	Pharmacokinetics
PKC	Protein kinase C
PML	Progressive multifocal leukoencephalopathy
PMBCL	Primary mediastinal large B-cell lymphoma
PRAS40	Proline-rich AKT substrate of 40 kDa
PT	Prothrombin time
PT/INR	Prothrombin time/international normalized ratio
PTEN	Phosphatase and tensin homologue
PTT	Partial thromboplastin time

Abbreviation or special term	Explanation
Q3M	Every 3 months
qd	Once daily dosing
QM	Every month
QTc	QT interval
QTcF	QT interval corrected by Fridericia's formula
R/R	Relapsed/refractory
Randomization	Randomization applies only to Part 1 of this study and will be used to randomly assign subjects to either Schedule 1 or Schedule 2 of vistusertib.
R-CHOP	Rituximab + cyclophosphamide, doxorubicin, vincristine, and prednisone
RECIST	Response Evaluation Criteria In Solid Tumors
Rheb	Ras homolog enriched in brain
RS	Richter syndrome
S6K	S6 kinase
SAE	Serious adverse event
Schedule 1	Continuous (ie, daily) dosing schedule for vistusertib
Schedule 2	Intermittent (ie, 2 days on/5 days off) dosing schedule for vistusertib.
SD	Stable disease
SDi	Shortest axis perpendicular to the longest transverse diameter of a lesion
SFU	Safety follow-up
SGK	Serine/threonine-protein kinase
SLL	Small lymphocytic lymphoma
SOC	Standard of care

Abbreviation or special term	Explanation
SPD	Sum of the product of the perpendicular diameters for multiple lesions.
SREBP	Sterol regulatory element-binding protein
SUSAR	Suspected unexpected serious adverse reaction
SYK	Spleen tyrosine kinase
$t_{½}$	Half-life
TBL	Total bilirubin
TEAEs	Treatment-emergent adverse events
T_{max}	Time of the maximum plasma concentration
TSC	Tuberous sclerosis protein
ULN	Upper limit of normal
V_z/F	Oral volume of distribution
WHO	World Health Organization
WHODRUG	World Health Organization Drug Dictionary
WM	Waldenström macroglobulinemia

STUDY SYNOPSIS

Protocol Number:	ACE-LY-110
Study Drugs:	Acalabrutinib (ACP-196) and vistusertib (AZD2014)
Protocol Title:	A Phase 1/2 Proof-of-Concept Study of the Combination of Acalabrutinib and Vistusertib in Subjects with Relapsed/Refractory B-cell Malignancies
Phase:	Phase 1/2
Comparator:	None
Background and Rationale for Study	Decades of research across various oncologic diseases support the fact that multidrug regimens (eg, polychemotherapy and chemoimmunotherapy) produce higher and more durable complete response (CR) rates than single-agent chemotherapy. However, these benefits are often outweighed with the increased toxicity associated with multidrug regimens. The high risk:benefit ratio of multidrug regimens means these regimens are less likely to be used in elderly patients or patients with comorbid conditions. The advent of highly selective, targeted agents to treat B-cell malignancies, such as B-cell receptor (BCR) signaling antagonists, has changed the risk:benefit paradigm traditionally associated with chemotherapy agents. When administered as single agents, BCR antagonists have produced high objective overall response rates (ORR) in some patients with B-cell malignancies. For example, ibrutinib, a small molecule inhibitor of Bruton tyrosine kinase (BTK), has been approved for the treatment for chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL) and Waldenström macroglobulinemia (WM). In addition, ibrutinib has shown clinical efficacy in other B-cell malignancies including follicular lymphoma (FL); (Advani et al 2012) and transformed diffuse large B-cell lymphoma (DLBCL); (Wilson et al 2015, Ayers & Mato 2016). However, the proportion of patients with CRs, when treated with BCR signaling antagonists as monotherapy, is low compared with traditional polychemotherapy or chemoimmunotherapy (Advani et al 2012, Blum 2015). Also, in more aggressive histologies the median duration of response (DOR) can be low (<12 months) (Blum 2015). The question remains whether “targeted combination” therapy can produce more durable responses and potentially more CRs than single agents without an undue associated increase in toxicity. Acerta Pharma is developing acalabrutinib as an orally administered, small molecule inhibitor of BTK. Preclinical data indicate that acalabrutinib may offer greater potency, improved selectivity, better pharmaceutical properties, and less potential for

	drug-drug interactions than ibrutinib. Acalabrutinib has shown clinical activity in an ongoing Phase 1 study in subjects with CLL (CCI; Byrd et al 2016) and Richter syndrome (RS) (Hillmen et al 2016) and in an ongoing Phase 2 study in subjects with relapsed/refractory MCL (Wang et al 2017). AstraZeneca is developing a novel, oral, mammalian target of rapamycin (mTOR) inhibitor, vistusertib, which has shown in vitro and in vivo activity across a range of preclinical human cancer models. In contrast to everolimus, temsirolimus or other rapalogs, which are solely mTORC1 inhibitors, vistusertib has a distinct mechanism of action as a dual mTORC1 and mTORC2 inhibitor. mTOR is part of the multiprotein complexes mTORC1 and mTORC2, which have been shown to play critical yet functionally distinct roles in the regulation of cellular processes. A first-in-human study of vistusertib has been conducted in subjects with advanced solid tumors (NCT01026402; Basu et al 2016) and several Phase 1 and 2 studies are currently being conducted. Pharmacodynamic analyses of the subject samples from the first-in-human study showed inhibition of phosphorylation of S6 and protein kinase B (AKT) providing evidence for mTORC1 and mTORC2 inhibition, respectively. Preliminary findings from an ongoing Phase 2 study (CCI) evaluating vistusertib monotherapy in DLBCL appear to show acceptable tolerability and activity in DLBCL. The mechanism of action of vistusertib suggests the potential to combine it with a number of anticancer treatments, including BTK inhibitors. The multiplicity of mechanisms involved in transducing signals from the BCR and the existence of multiple negative feedback loops support the hypothesis that inhibiting BTK signaling together with inhibition of mTORC1/2 may deliver clinical benefit. In support of this theory, preclinical studies using a DLBCL cell line have shown greater efficacy when combining vistusertib with either ibrutinib or acalabrutinib compared with each agent administered alone. This proof-of-concept study will assess the clinical potential of a dual BTK and mTORC1/2 inhibition approach by evaluating the safety, pharmacokinetics (PK), pharmacodynamics (PD) and efficacy of acalabrutinib and vistusertib in relapsed/refractory subsets of B-cell malignancies.
Study Design:	This study is a multicenter, open-label, randomized (Part 1 only) parallel group study to be conducted at approximately 15 to 20 sites. The study *was originally designed to be* divided into 2 parts. The Phase 1 portion of the study (Part 1) evaluate*d* the safety, PK, and PD of combining acalabrutinib 100 mg twice a day (bid) and vistusertib (various doses and schedules). Part 1 *was to* be used to select the vistusertib dose and schedule for Phase 2. The Phase 2 portion of the study (Part 2) *was to* allow for expansion groups in select B-cell histologies to further evaluate safety,

efficacy, and PKPD of the combination treatment*; however, the sponsor has decided to close the study prior to initiating Part 2*.

Part 1

Part 1 of the study will include adult subjects with any of the following relapsed/refractory disease types:

- De novo DLBCL
- Transformed DLBCL
- Richter syndrome (RS)

Subjects will take acalabrutinib twice per day at approximately 12-hour intervals. A treatment cycle is defined as 28 days. The acalabrutinib dose will be 100 mg bid. Acalabrutinib is administered on every day of the 28-day cycle. Section 3.2 of the protocol provides the rationale for the study design and the rationale for the vistusertib dose and schedules evaluated in this protocol. The study schema is presented in Figure 2.

Although acalabrutinib monotherapy has not demonstrated dose-limiting toxicities (DLTs) to date, the safety of the combination of acalabrutinib and vistusertib in this patient population needs to be assessed. Therefore, a safety analysis (see Section 3.14) will occur when 6 subjects have been enrolled in each schedule (see below). Eligible subjects will be randomized (1:1) to Schedule 1 or Schedule 2, Level -1 for both, using an Interactive Voice/Web Response System (IXRS).

The following doses/schedules for vistusertib will be evaluated in combination with acalabrutinib 100 mg bid in Part 1:

	Level -1 (Starting Dose)	**Target Level**	**Level +1**
Continuous dosing schedule (**Schedule 1**)	35 mg bid (daily) n=6	50 mg bid (daily) n=6	75 mg bid (daily) n=6
Intermittent dosing schedule (**Schedule 2**)	100 mg bid (2 days on/5 days off) n=6	125 mg bid (2 days on/5 days off) n=6	150 mg bid (2 days on/5 days off) n=6

Abbreviations: bid = twice per day

Standard DLT criteria (defined below) will be used to assess safety of the combination during the first cycle of treatment. Each schedule is independently assessed. Escalation to the next level cannot occur until the DLT review as occurred. If ≤1 DLTs occur during cycle 1 in the 6 subjects enrolled in a given schedule, then the dose of vistusertib will be escalated as outlined above and

	6 new subjects will be enrolled and assessed for DLT. Detailed information on DLT review and toxicity monitoring is provided in Section 3.7 and Section 3.14 of the protocol. The safety and PKPD results of subjects treated in Part 1 *were to* be used to select the vistusertib dose/schedule for Part 2. Any DLTs attributed to the combination after cycle 1 *were* also *to* be taken into consideration when determining the vistusertib dose and schedule for Part 2. *Amendment 2 of this protocol added a higher dose level of vistusertib (Level +1) to Part 1 of the protocol. However, as mentioned previously, the sponsor stopped the study after evaluating the efficacy, safety, PD, and PK data from the subjects treated with the lower dose levels of vistusertib.* **Part 2** Part 2 *was designed to* consist of expansion groups of 15 or 20 subjects per histology (N≤35 total for Part 2) provided the safety results from Part 1 of the study indicated that further evaluation of the combination *was* warranted. *As mentioned above, the study was closed before initiating Part 2.* Subjects showing clinical benefit (ie, no disease progression) and who are tolerating study treatment may remain on study for up to a total of 12 cycles of treatment. Subjects who have received 12 cycles of treatment (ie, been on study for approximately 12 months) and are deriving clinical benefit from acalabrutinib monotherapy or the combination of acalabrutinib and vistusertib may *remain on study treatment beyond the first 12 months until disease progression occurs or* be eligible to enroll in either a rollover study of acalabrutinib monotherapy or a rollover study of the combination of acalabrutinib and vistusertib, respectively. The schedule of assessments for combination treatment is provided in Appendix 1 and for acalabrutinib monotherapy is provided in Appendix 2.
Definition of Dose-limiting Toxicity:	Throughout the study, severity of adverse events (AEs) will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE). For Part 1, a DLT will be defined as the occurrence of any of the following AEs (Note that all AEs of the specified grades should be recorded as DLTs with the exception of those that are clearly, and incontrovertibly, due to extraneous causes such as disease progression): 1. Any Grade ≥3 nonhematologic toxicity except Grade 3 nausea, vomiting, or diarrhea that respond to supportive therapy (eg, improvement by 1 or more severity grade within 48 hours). 2. Any of the following hematologic toxicities:

	a. Grade 4 neutrophil count decrease lasting >7 days, despite growth factor support b. Grade 4 platelet count decrease or Grade 3 platelet count decrease with bleeding c. Grade ≥3 febrile neutropenia d. Grade 4 anemia, unexplained by underlying disease 3. Clinical tumor lysis syndrome (TLS) (defined in Table 3) that occurs despite protocol-recommended management will be considered a DLT. 4. Laboratory TLS (defined in Table 4) will be considered a DLT if the metabolic abnormalities do not resolve within 72 hours despite protocol-required management. 5. Dosing delay due to drug-related toxicity for >28 consecutive days A DLT excludes: 1. Alopecia of any grade 2. Isolated laboratory changes of any grade without clinical sequelae or clinical significance
Study Objectives:	**Primary Objectives:** Part 1 Objective: To determine a dose and schedule for vistusertib in combination with acalabrutinib 100 mg bid for evaluation in Part 2 Part 2 Objective: To evaluate the safety of acalabrutinib and vistusertib when coadministered **Secondary Objectives:** • To evaluate the PK of acalabrutinib and vistusertib when coadministered • To evaluate the clinical activity of acalabrutinib and vistusertib, when coadministered, as measured by ORR, including CR rate, DOR, durable response rate (DRR), progression-free survival (PFS) and overall survival (OS) **Exploratory Objectives:** • CCI [redacted]

	CCI 
Safety Parameters:	Type, frequency, severity, and relationship to study drug of any treatment-emergent adverse events (TEAEs) or abnormalities of laboratory tests, serious adverse events (SAEs), DLTs or AEs leading to discontinuation of study drug(s).
Pharmacokinetic Parameters:	The plasma PK of acalabrutinib and vistusertib will be characterized using noncompartmental analysis. The following PK parameters will be calculated, whenever possible, from plasma concentrations of analytes *(Note: These will not be collected or assessed for subjects whose study participation extends past the first 12 cycles.)*: • $AUC_{0\text{-last}}$: Area under the plasma concentration-time curve calculated using linear trapezoidal summation from time 0 to time last, where "last" is the time of the last measurable concentration • $AUC_{0\text{-inf}}$: Area under the plasma concentration-time curve from 0 to infinity, calculated using the formula: $AUC_{0\text{-inf}} = AUC_{0\text{-last}} + C_{last} / \lambda_z$, where λ_z is the apparent terminal elimination rate constant • C_{max}: Maximum observed plasma concentration • T_{max}: Time of the maximum plasma concentration (obtained without interpolation) • $t_{½}$: Terminal elimination half-life (whenever possible) • λ_z: Terminal elimination rate constant (whenever possible) • CL/F: Oral clearance

	• V_z/F: Oral volume of distribution
Pharmacodynamic Parameters:	The occupancy of BTK by acalabrutinib will be measured in peripheral blood mononuclear cells (PBMCs) with the aid of an acalabrutinib analogue probe. The effect of acalabrutinib and vistusertib on biologic markers of B-cell function will also be evaluated in PBMCs and/or tumor tissue. Cell populations will be monitored for effect of treatment, which may include, but are not limited to, leukocyte or lymphocyte subsets (eg, T, B and natural killer [NK] cells) and their activation states. Additional PD markers include, but are not limited to, pS6, pBTK, pAKT, p4EBP1 and pPLCγ2.
Efficacy Parameters:	• ORR (CR + PR) • DRR • CR rate • DOR • PFS • OS Analysis of efficacy parameters is provided in Section 5.5.4. *The efficacy evaluations will not be assessed for subjects whose study participation extends past the first 12 cycles.*
Sample Size:	A maximum of 3 dose levels *were to have been* explored in each of the two schedules (continuous/intermittent vistusertib dosing). The maximum number of subjects in Part 1 *was* therefore 36. *The sponsor stopped the study in Part 1 after treating 25 subjects with the first 2 dose levels of vistusertib*.
Inclusion Criteria:	1. Diagnosis of relapsed/refractory DLBCL as documented by medical records and with histology based on criteria established by WHO: a. If a subject has de novo DLBCL, the diagnosis is confirmed by biopsy and is immunohistologically characterized as de novo non-GCB DLBCL or de novo GCB DLBCL. Note that primary mediastinal B-cell lymphoma (PMBCL) is excluded from this protocol. **Tumor tissue must also be available for sending to the sponsor for central cell of origin testing.** b. If the subjects has RS, the diagnosis is confirmed by biopsy and is immunohistologically characterized as transformation to DLBCL. **Tumor tissue must also be available for sending to the sponsor for central pathology testing. This histology applies to Part 1 only.** c. If the subjects has transformed DLBCL, the diagnosis is confirmed by biopsy and is immunohistologically

	characterized as transformation to DLBCL from indolent lymphoma (eg, follicular lymphoma). **Tumor tissue must also be available for sending to the sponsor for central pathology testing. This histology applies to Part 1 only.** 2. Men and women ≥18 years of age. 3. Prior treatment for lymphoid malignancy: a. If the subject has DLBCL, there is no curative option with conventional therapy and the prior treatment included ≥1 prior combination chemoimmunotherapy regimen (eg, anthracycline-based therapy with rituximab, such as rituximab + cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP]). Also subjects should have relapsed after autologous stem cell transplant [ASCT] or should be noncandidates for ASCT. b. If the subject has RS, the subject must have had ≥1 prior treatment with a combination chemoimmunotherapy regimen. 4. Presence of radiographically measurable lymphadenopathy or extranodal lymphoid malignancy (defined as the presence of a ≥1.5 cm lesion, as measured in the longest dimension by computed tomography [CT] scan for all histologies). 5. Documented active disease that is relapsed or refractory defined as: a. Relapse: disease progression after completion of the treatment regimen preceding entry into the study. b. Refractory: progressive disease or stable disease as best response at any point during chemotherapy (>4 cycles of first-line or 2 cycles of later-line therapy) or relapsed at ≤12 months from autologous stem cell transplantation (Crump et al 2017). 6. Eastern Cooperative Oncology Group (ECOG) performance status of ≤2. 7. Adequate hematologic function, independent of transfusion and growth factor support for ≥14 days before screening, defined as: a. Absolute neutrophil count (ANC) >1000 cells/mm^3 (1.0×10^9/L) b. Platelet count >75,000 cells/mm^3 (75×10^9/L) or >50,000 cells/mm^3 with bone marrow involvement c. Hemoglobin >8.0 g/dL 8. Adequate hepatic and renal function at screening defined as: a. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 x upper limit of normal (ULN) if no demonstrable liver involvement or ≤3 x ULN in the presence of liver metastases

	b. Bilirubin ≤1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin) c. Serum creatinine ≤1.5 times ULN and creatinine clearance >30 mL/min (measured or calculated by Cockcroft and Gault equation [(140-Age) • Mass (kg)/(72 • creatinine mg/dL) • multiply by 0.85 if female]) 9. Prothrombin time/international normalized ratio (PT/INR) <1.5 x ULN and activated partial thromboplastin time (aPTT) <1.5 x ULN. 10. Serum potassium within normal range. 11. Women should be using adequate contraceptive measures, should not be breast feeding and must have a negative pregnancy test before start of dosing if of child-bearing potential or must have evidence of nonchildbearing potential by fulfilling one of the following criteria at screening: a. Postmenopausal women, defined as either women aged >50 years and amenorrheic for ≥12 months following cessation of all exogenous hormonal treatments, or, women under 50 years old who have been amenorrheic for ≥12 months following the cessation of exogenous hormonal treatments, and have serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels in the postmenopausal range for the institution. b. Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation. c. Medically confirmed, irreversible premature ovarian failure. Women who are sexually active and of childbearing potential must be willing to use 2 forms of contraception (see Section 3.11.7) from the time of screening to 90 days after discontinuing study drug(s). 12. Men *who are sexually active must* use barrier contraception (ie, condoms) *in addition to the highly effective contraception* and refrain from sperm donation during the study and *until 2* days after *the subject's last dose of acalabrutinib or 16 weeks after the subject's last dose of vistusertib, whichever is longer*. If not done previously, storage of sperm before receiving vistusertib will be advised to male subjects with a desire to have children. 13. Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules/tablets without difficulty. 14. Willing to follow sunlight protection measures while taking vistusertib (eg, using sunscreen and avoiding excessive sun exposure) and for 90 days after the last dose of vistusertib. 15. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization

	to use protected health information (in accordance with national and local patient privacy regulations). **Host genetics research study (optional):** For inclusion in the optional genetic component of the study, subjects must fulfil the following additional criteria: 16. Provision of signed, written, and dated informed consent for genetic research. If a subject declines to participate in the genetic component of the study, there will be no penalty or loss of benefit to the subject. The subject will not be excluded from other aspects of the study described in this protocol, so long as they consented to the main study. 17. Whole blood transfusion given within 120 days of genetic sample collection should be leukocyte depleted. **Tumor biopsy study (optional):** For inclusion in the optional tumor biopsy component of the study, subjects must fulfil the following additional criteria: 18. Provision of signed, written, and dated informed consent for fresh lymph node tumor biopsies (at baseline, on study and at progression). If a subject declines to participate in the tumor biopsy component of the study, there will be no penalty or loss of benefit to the subject. The subject will not be excluded from other aspects of the study described in this protocol, so long as they consented to the main study. 19. Presence of superficial lymphadenopathy for the lymph node biopsy.
Exclusion Criteria:	**<u>All Parts:</u>** 1. History of prior malignancy except for the following: a. Malignancy treated with curative intent and with no evidence of active disease present for more than 2 years before screening and felt to be at low risk for recurrence by treating physician. b. Adequately treated lentigo maligna melanoma without current evidence of disease or adequately controlled nonmelanomatous skin cancer. c. Adequately treated carcinoma in situ without current evidence of disease. 2. As judged by the Investigator, any evidence of severe or uncontrolled systemic disease (eg, severe hepatic impairment, interstitial lung disease [bilateral, diffuse, parenchymal lung disease]), or current unstable or uncompensated respiratory or cardiac conditions, or uncontrolled hypertension, history of, or active, bleeding diatheses (eg, hemophilia or von Willebrand disease) or uncontrolled active systemic fungal, bacterial, viral, or other infection (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other

	treatment), or intravenous anti-infective treatment within 2 weeks before first dose of study drug. 3. Diagnosis of PMBCL. 4. Known history of infection with human immunodeficiency virus (HIV). 5. Serologic status reflecting active hepatitis B or C infection. a. Subjects who are hepatitis B core antibody positive (anti-HBc) and who are surface antigen negative will need to have a negative polymerase chain reaction (PCR) result before enrollment. Those who are hepatitis B surface antigen positive or hepatitis B PCR positive will be excluded. b. Subjects who are hepatitis C antibody positive will need to have a negative PCR result before enrollment. Those who are hepatitis C PCR positive will be excluded. 6. Active cytomegalovirus (CMV) infection (positive CMV immunoglobulin M [IgM] and/or positive PCR result) 7. Undergone any of the following procedures or experienced any of the following conditions currently or in the preceding 6 months: a. coronary artery bypass graft b. angioplasty c. vascular stent d. myocardial infarction e. angina pectoris f. congestive heart failure (New York Heart Association [NYHA] Grade ≥2) g. ventricular arrhythmias requiring continuous therapy h. supraventricular arrhythmias, including atrial fibrillation, which are uncontrolled i. hemorrhagic or thrombotic stroke, including transient ischemic attacks or any other central nervous system bleeding. 8. Current refractory nausea and vomiting, malabsorption syndrome, disease significantly affecting gastrointestinal (GI) function, resection of the stomach, extensive small bowel resection that is likely to affect absorption, symptomatic inflammatory bowel disease, partial or complete bowel obstruction, or gastric restrictions and bariatric surgery, such as gastric bypass. 9. History of central nervous system (CNS) lymphoma, leptomeningeal disease or spinal cord compression. 10. History of severe allergic or anaphylactic reactions to kinase inhibitors or history of hypersensitivity to active or inactive excipients of vistusertib or acalabrutinib or drugs with a similar chemical structure or class to vistusertib or acalabrutinib.

	11. Presence of a GI ulcer diagnosed by endoscopy within 3 months before screening. 12. Uncontrolled Type 1 or Type 2 diabetes mellitus (eg, hemoglobin A1c ≥7%). 13. Any clinically significant pre-existing severe renal disease (eg, glomerulonephritis, nephritic syndrome, Fanconi Syndrome or renal tubular acidosis) or high risk of developing severe renal impairment. 14. Major surgical procedure within 28 days before first dose of study drug. Note: If a subject had major surgery, they must have recovered adequately from any toxicity and/or complications from the intervention before the first dose of study drug. 15. Unresolved toxicities from prior anticancer therapy, defined as having not resolved to CTCAE [Version **5.0**] Grade 0 or 1, or to the levels dictated in the inclusion/exclusion criteria, with the exception of alopecia. 16. Any hematopoietic growth factors (eg, filgrastim [granulocyte colony-stimulating factor; G-CSF], sargramostin [granulocyte-macrophage colony-stimulating factor; GM-CSF]) within 7 days of the first dose of study drug or pegylated G-CSF (pegfilgrastim) or darbepoetin within 14 days of the first dose of study drug. 17. Vaccinated with live, attenuated vaccines within 4 weeks of first dose of study drug. 18. Abnormal echocardiogram (ECHO) or multi-gated acquisition scan (MUGA) at baseline (left ventricular ejection fraction [LVEF] <40% and shortening fraction <15%). Appropriate correction to be used, if a MUGA is performed. 19. Mean resting corrected QT interval (QTc) calculated using Fridericia's formula (QTcF) >450 msec obtained from 3 electrocardiograms (ECGs); family or personal history of long or short QT syndrome; Brugada syndrome or known history of QTc prolongation or torsade de pointes within 12 months of the subject entering the study. 20. Factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, or family history of sudden unexplained death under 40 years of age. Concomitant medications known to prolong QTc should be used with caution and cannot be used during the first 28 days on study. 21. Any therapeutic antibody within 4 weeks of first dose of study drugs. 22. Prior use of standard antilymphoma therapy or radiation therapy within 14 days of receiving the first dose of study drug (not including palliative radiotherapy). Subjects must have recovered from acute toxicity due to prior treatment. Note: Subjects previously treated with BTK, mTOR or phosphoinositide 3 kinase (PI3K) inhibitors are not excluded

	from this protocol; however, the 14-day washout and recovery from acute toxicity from these agents still applies. 23. Ongoing immunosuppressive therapy, including systemic (eg, intravenous or oral) corticosteroids for treatment of lymphoid cancer or other conditions. Note: Subjects may use topical or inhaled corticosteroids or low-dose steroids (≤10 mg of prednisone or equivalent per day) as therapy for comorbid conditions. During study participation, subjects may also receive systemic corticosteroids as needed for treatment-emergent comorbid conditions. 24. Exposure to strong or moderate inhibitors or inducers of cytochrome P450 (CYP) 3A4/5, permeability glycoprotein (P-gp), or breast cancer resistance protein (BCRP), if taken within the stated washout periods before the first dose of study drug (see Appendix 4). 25. Exposure to specific substrates of the drug transporters OATP1B1, OATP1B3, MATE1 and MATE2K within the appropriate washout period for each drug (a minimum of 5 x reported elimination half-life) before the first dose of study drug (see Appendix 4). 26. Requires or receiving therapeutic anticoagulants, with the exception of short-acting heparins, within 7 days of first dose of study drug. 27. Requires treatment with proton-pump inhibitors (eg, 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. 28. Recent history (past 12 months) of drug abuse or alcohol abuse, as judged by the investigator. 29. Concurrent participation in another therapeutic clinical trial.
Dosage Form and Strength:	Acalabrutinib drug product is provided as hard gelatin capsules for oral administration. The capsules contain 100 mg of acalabrutinib. Vistusertib drug product is provided as round or oval, film-coated tablets for oral administration. Tablets contain either 25, 35 or 50 mg of vistusertib.
Dose Regimen/Route of Administration:	Acalabrutinib and vistusertib are orally administered products. Both drugs will be administered concomitantly. On dosing days, each drug is administered bid and should be administered approximately 12 hours apart. The regimens evaluated in this protocol are specified in the study design section.
Concomitant Medications:	Subjects should avoid the use of calcium carbonate containing drugs or supplements for a period of ≥2 hours before and ≥2 hours after taking acalabrutinib. Use of omeprazole, esomeprazole, lansoprazole or any other proton-pump inhibitors while taking

	acalabrutinib is not recommended due to a potential decrease in study drug exposure. Although the effect of H2-receptor antagonists (such as famotidine or ranitidine) on acalabrutinib absorption has not been evaluated, if treatment with an H2-receptor antagonist is required, the H2-receptor antagonist should be taken approximately 2 hours after an acalabrutinib dose. Use of concomitant medications which are moderate or strong inhibitors or inducers of CYP3A4/5, P-gp and BCRP, or specific substrates of the drug transporters OATP1B1, OATP1B3, MATE1 and MATE2K should be avoided when possible. Detailed information on short-term concomitant administration of these drugs is provided in the protocol. Details on permitted and required concomitant medications are provided in the protocol.
Statistics:	Descriptive statistics (including means, standard deviations, and medians for continuous variables and proportions and confidence intervals [CIs] for discrete variables) will be used to summarize data as appropriate. Response rate will be investigator assessed using standard response criteria (Cheson et al 2014; see Appendix 9). Kaplan-Meier (KM) methods will be used to estimate DOR, PFS, and OS and corresponding quartiles (including the median). The primary objective of this study is evaluating the safety of acalabrutinib 100 mg bid with vistusertib (either continuous dosing or intermittent dosing). The objective of Part 1 is to select a vistusertib dose and regimen for the Phase 2 portion of the study (Part 2). In Part 1 (DLT assessment), 12 to 36 subjects will be enrolled to evaluate different dose levels and schedules of vistusertib. In Part 2 (expansion groups), enrollment of approximately 15 or 20 subjects per histology (approximately N=35 total) *was to* offer the opportunity to evaluate further the safety and PKPD of the chosen dose/schedule for vistusertib from Part 1. *However, the sponsor has decided to close the study prior to initiating Part 2.*

1.0 BACKGROUND INFORMATION

Note the information provided in this section of the protocol represents the most up to date information available when the protocol was being drafted. For the most up to date information, particularly with regard to clinical safety information, please refer to the most recent version of the Acalabrutinib Investigator Brochure or the Vistusertib Investigator Brochure.

1.1 ACALABRUTINIB (ACP-196)

Acalabrutinib is (S)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)-imidazo[1,5-α]pyrazin-1-yl)-N-(pyridin-2-yl)-benzamide. Acalabrutinib is a selective, irreversible small molecule BTK inhibitor. Acalabrutinib is also known as ACP-196.

The first BTK inhibitor developed for clinical use, ibrutinib (IMBRUVICA®), has been approved in the United States and Europe for the treatment of CLL/SLL, MCL and WM. Ibrutinib also has recently been approved in the United States for MZL. While potent in inhibiting BTK, ibrutinib has also shown in vitro activity against other kinases with a cysteine (Cys) in the same relative position as Cys481 of BTK, to which the drug covalently binds (Honigberg et al 2010). These off-target activities may contribute to the toxicity profile observed for ibrutinib (Warnings and Precautions, ibrutinib prescribing information) and could lead to discontinuation of ibrutinib. In addition, ibrutinib is primarily metabolized by CYP3A. Thus, ibrutinib dosing must be halted or reduced when coadministered with drugs that are strong or moderate inhibitors of CYP3A (ibrutinib prescribing information). Recent data suggest ibrutinib treatment breaks (eg, treatment breaks >14 days including discontinuation) negatively impact overall survival in patients with CLL (UK CLL Forum 2016). Therefore, development of alternative BTK inhibitors is needed for the treatment of B-cell malignancies.

Acerta Pharma is developing acalabrutinib for the treatment of patients with cancer. Acalabrutinib is orally administered in humans and is suitable for formulating in capsules. For clinical testing, acalabrutinib has been manufactured and formulated according to current Good Manufacturing Practices (cGMP).

Acalabrutinib (CALQUENCE®) *has been* approved in the United States *and other markets* for the treatment of *adult* patients with MCL who have *received* at least 1 prior therapy (CALQUENCE package insert).

1.1.1 Safety Pharmacology and Toxicology

In vitro and in vivo safety pharmacology and toxicology studies with acalabrutinib have demonstrated a favorable nonclinical safety profile; for detailed information, refer to the Acalabrutinib Investigator Brochure.

1.1.2 Drug-drug Interaction Potential

For detailed information on drug-drug interaction potential for acalabrutinib, refer to the Acalabrutinib Investigator Brochure. Please refer to Section 3.11.5 of this protocol for guidance on drugs that may cause drug-drug interactions.

1.1.3 Clinical Experience

As of 03 September 2017, acalabrutinib has been administered to over 2000 participants in clinical studies, including subjects with hematologic malignancies, solid tumors, or rheumatoid arthritis, and participants who are healthy volunteers or with mild to moderate hepatic impairment. No SAEs have been reported in the hepatic impairment study or in the healthy volunteer studies. No DLTs have been identified in any studies for acalabrutinib monotherapy or in combination with other agents. Identified risks for acalabrutinib include bleeding events (eg, epistaxis, bruising, and hematoma), headaches, gastrointestinal events (eg, diarrhea and nausea/vomiting), and rash; all mostly low grade and nonserious. For detailed information on the clinical experience for acalabrutinib, please refer to the Acalabrutinib Investigator Brochure.

Preliminary efficacy data are summarized below from ACE-CL-001 (CCI [redacted]), an ongoing nonrandomized, sequential group, dose-escalation Phase 1/2 study in subjects with relapsed/refractory or previously untreated CLL, RS or prolymphocytic leukemia.

As of 01 October 2015, 60 subjects with relapsed CLL have been evaluated for tumor response based on modified International Working Group response criteria (Hallek et al 2008) as recently updated (Cheson et al 2012) to include PR with treatment-induced lymphocytosis. With a median follow up of 14.3 months, an ORR of 95% has been observed (Byrd et al 2016). Few subjects have had disease progression.

As of 28 February 2017, 124 subjects with relapse/refractory MCL treated with acalabrutinib 100 mg twice per day (bid) have been evaluated for tumor response using the Lugano Classification (Cheson et al 2014). At a median follow-up of 15.2 months, 100 (81%) subjects achieved an overall response and 49 (40%) subjects achieved a complete response (Wang et al 2017). The Kaplan-Meier estimated medians for duration

of response, progression-free survival, and overall survival were not reached; the 12-month rates were 72% (95% CI 62–80), 67% (58–75), and 87% (79–92%), respectively (Wang et al 2017).

1.2 VISTUSERTIB (AZD2014)

Vistusertib, also known as AZD2014, is an inhibitor of mTOR kinase, which plays a critical role in regulating cellular energy sensing, growth and metabolism. Deregulation of mTOR signaling is observed in many tumors types (Chiarini et al 2015; Xu et al 2014), and mutations or loss of function of upstream regulators have been reported in most types of human tumors (Thorpe et al 2015; Martini et al 2014). The PI3K/AKT/mTOR cellular signaling pathway is summarized in Figure 1.

The mTOR kinase forms 2 distinct multiprotein complexes called mTORC1 and mTORC2. The mTORC1 complex plays a key role in coupling nutrient sensing with the regulation of protein translation and cellular metabolism processes. It directly phosphorylates proteins such as p70S6K (S6K) (Magnuson et al 2012) and 4E-BP1 (Hsieh et al 2010), which are involved in controlling cellular growth and proliferation, as well as sterol regulatory element-binding protein (SREBP) (Bakan & Laplante 2012), a key modulator of metabolism and lipid synthesis. The mTORC1 complex also phosphorylates a number of substrates that modulate autophagy and lysosome biogenesis (Betz & Hall 2013). The mTORC2 complex has been reported to play a role in the cellular response to extracellular growth factors through largely unknown mechanisms. Its activation requires association with ribosomes and results in the phosphorylation of downstream targets such as the AGC family of protein kinases, which includes AKT, serine/threonine-protein kinase (SGK), and protein kinase C (PKC) (Su & Jacinto 2011).

Rapamycin and its analogues (rapalogues) are potent inhibitors of mTORC1 and have been shown to be clinically effective in certain cancer types such as endometrial cancer, MCL, DLBCL, FL, renal cell carcinoma, and breast cancer (Faivre et al 2006; Witzig et al 2005; Witzig et al 2011, Baselga et al 2012). However, resistance to rapamycin and its analogues has been shown to limit their response rates in clinical studies.

Vistusertib is a selective inhibitor of mTOR kinases and, unlike rapalogues, inhibits signaling of mTORC1 and mTORC2 complexes (Guichard et al 2015). Vistusertib is therefore molecularly differentiated from rapamycin and its analogues (eg, everolimus and temsirolimus), which are solely mTORC1 inhibitors. In addition to its dual inhibition

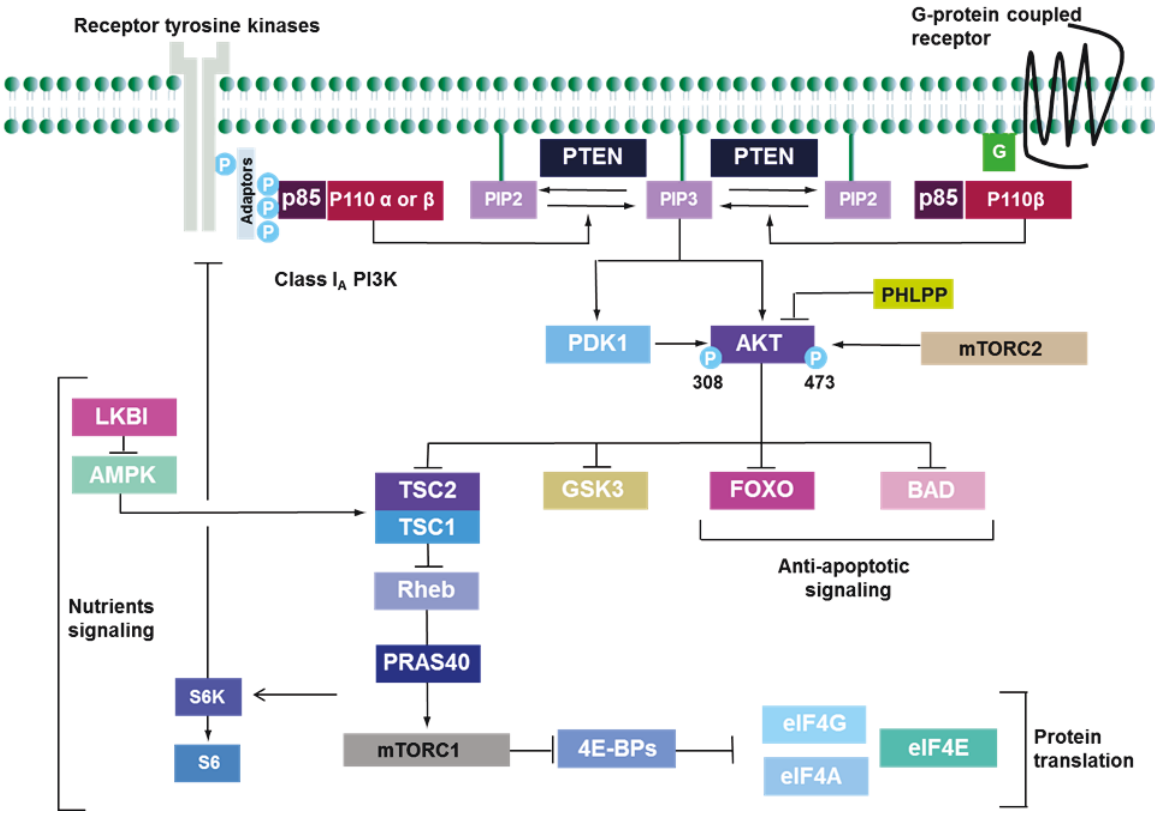
of mTORC1 and mTORC2, vistusertib achieves a more profound inhibition of mTORC1 and shows a broader range of growth inhibitory activity in vitro across tumors types compared with rapalogues.

While early clinical data using allosteric mTORC1 inhibitors have suggested some activity in a number of hematologic diseases, these agents have shown limited efficacy as monotherapies. However, the multiplicity of mechanisms involved in transducing signals from the BCR and the existence of multiple negative feedback loops, suggests that inhibition of BTK in combination with inhibition of mTOR may deliver clinical benefit in BCR driven cancers (Lee et al 2016).

AstraZeneca is developing vistusertib for the treatment of patients with cancer. Vistusertib is orally administered in humans and is suitable for formulating in tablets. For clinical testing, vistusertib has been manufactured and formulated according to current cGMP.

Vistusertib is an investigational product and has not been approved for marketing in any country. Further details are provided in the Vistusertib Investigator Brochure.

Figure 1. PI3K/AKT/mTOR pathway



Simplified scheme of the mTOR signaling network. Signals from diverse extra- and intracellular cues (such as growth factors, stress, energy, and nutrients) are sensed and integrated by the output of the two functionally distinct complexes — mammalian target of rapamycin complex 1 (mTORC1) and mTORC2 — to deliver a coordinated cellular response. Abbreviations: AKT, protein kinase B ;4EBP1, eukaryotic translation initiation factor 4E (eIF4E)-binding protein 1; AMPK, AMP-activated protein kinase; BAD Bcl-2-associated death promoter; FOXO Forkhead box protein O1; GSK3, Glycogen synthase kinase 3; PDK1, phosphoinositide-dependent protein kinase 1; PHLPP, PH domain and leucine rich repeat protein phosphatases; PI3K, phosphoinositide 3 kinase; PIP, phosphatidylinositol phosphate; PRAS40, proline-rich AKT substrate of 40 kDa; PTEN, phosphatase and tensin homologue; Rheb, Ras homolog enriched in brain; S6K, S6 kinase; TSC, tuberous sclerosis protein.

1.2.1 Safety Pharmacology and Toxicology

In vitro and in vivo safety pharmacology and toxicology studies with vistusertib have demonstrated that vistusertib has an acceptable safety profile for administration to patients with cancer; for detailed information, refer to the Vistusertib Investigator Brochure.

1.2.2 Drug-drug Interaction Potential

For detailed information on drug-drug interaction potential for vistusertib, refer to the Vistusertib Investigator Brochure.

Please refer to Section 3.11.5 for guidance on drugs that may cause drug-drug interactions.

1.2.3 Clinical Experience

As of cut-off date of 05 October 2015, 547 subjects have been enrolled in studies with vistusertib; 252 in AstraZeneca-sponsored studies, and 295 in externally sponsored collaborative research (ESCR) studies. A total of 465 subjects have received vistusertib: 252 in AstraZeneca -sponsored studies and approximately 213 in ESCR studies.

Two AstraZeneca-sponsored Phase 1 studies were designed to assess the safety, tolerability, PK and preliminary efficacy of vistusertib: D2270C00001 (monotherapy in subjects with advanced cancer; the first-in-human study), and D2270C00005 (in combination with fulvestrant in subjects with metastatic breast cancer). Pharmacodynamic analyses of the subject samples from the first-in-human study (D2270C00001) showed inhibition of phosphorylation of S6 and protein kinase B (AKT) providing evidence for mTORC1 and mTORC2 inhibition, respectively (NCT01026402; Basu et al 2016). Study D2270C00001 is now complete and Clinical Study Report (CSR) is available, while study D2270C00005 is ongoing.

In addition, vistusertib has been administered as monotherapy to Japanese subjects with advanced solid malignancies in Study D2270C00005 (Japan PK) and to subjects with relapsed or refractory squamous non-small cell lung cancer after at least one line of therapy in combination with paclitaxel in Study D2274C00001 (STORK).

Several doses and dosing schedules of vistusertib have been explored in the monotherapy (D2270C00001) and combination (D2270C00005) studies:

Table 1. Vistusertib monotherapy (D2270C00001)

Dosing schedule	Doses explored	Defined MTD
Intermittent weekly bid dosing (2 consecutive days, 2 days on, 5 days off)	100 mg, 125 mg 170 mg, 225 mg	125 mg (2 consecutive days, 2 days on, 5 days off)
Continuous bid dosing	25 mg, 50 mg, 75 mg, 100 mg	50 mg
Continuous qd dosing	75 mg, 100 mg, 125 mg, 175 mg	100 mg

Abbreviations: bid = twice daily dosing; qd = once daily dosing; MTD = maximum tolerated dose.

Table 2. Vistusertib in combination with fulvestrant (D2270C00005)

Dosing schedule	Doses explored	Recommended dose/ defined MTD
Intermittent bid dosing (2 consecutive days, 2 days on 5 days off)	125 mg, 170 mg	125 mg (2 consecutive days, 2 days on 5 days off), under fasting and fed conditions
Continuous bid dosing	35 mg, 50 mg	50 mg
Continuous qd dosing	75 mg, 100 mg	75 mg

Abbreviations: bid = twice daily dosing; qd = once daily dosing; MTD = maximum tolerated dose.

Details of all vistusertib studies, including 10 ESCRs, are summarized in the Vistusertib Investigator Brochure.

Key Efficacy Findings for Vistusertib

Monotherapy

In the monotherapy study (D2270C00001) at the 50-mg bid dose in a total of 40 subjects, 2 subjects had an objective response; 1 subject with pancreatic acinar cell

type cancer and 1 subject with estrogen receptor positive breast cancer had confirmed PR according to Response Evaluation Criteria In Solid Tumors (RECIST) and received vistusertib treatment for 175 and 206 days, respectively. In addition, 12 subjects in the 50-mg bid group, and 4 subjects each in the 100-mg qd and 125-mg intermittent cohort achieved stable disease.

Combination with fulvestrant (Faslodex®)

For the combination study with fulvestrant (D2270C00005) information is included the Vistusertib Investigator Brochure on the best objective responses in all subjects and in subjects with measurable disease at baseline.

Based on data from 05 October 2015, vistusertib in combination with fulvestrant has demonstrated encouraging response rate data in this Phase 1 setting at maximum tolerated doses (MTDs) for the continuous and intermittent dosing schedules. There were PRs (confirmed and unconfirmed) at every MTD dose group: 3/11 (27%) with a confirmed response rate of 2/11 (18%) in the 50-mg bid continuous dosing group, 3/13 (23%) with a confirmed response rate of 2/13 (15%) in the 75-mg qd continuous dosing group, and 3/20 (15%) with a confirmed response rate of 1/20 (5%) in the 125-mg bid intermittent dosing group.

Key Safety Findings for Vistusertib

The overall safety findings at vistusertib MTDs in Phase 1 trials in monotherapy and in combination with fulvestrant were very similar and the main AEs observed are consistent with AEs already reported for other mTOR inhibitors: rash, pruritus, mucositis, fatigue, nausea, vomiting, diarrhea, constipation and decreased appetite.

Monotherapy

In Study D2270C00001, 87% of subjects experienced ≥1 AE considered related to vistusertib by the reporting investigator. The most common AEs related to study treatment (occurring in ≥15% subjects overall across all cohorts) were fatigue (59%), nausea (48%), mucositis (30%), diarrhea (28%), rash (27%), decreased appetite (22%), vomiting (22%) and hyperglycemia (16%). Dose-limiting toxicities (DLTs) reported at nontolerated doses were fatigue, diarrhea, mucositis, nausea, vomiting and rash. During the study, 55/135 (41%) subjects had an SAE, and 24/135 (18%) had a treatment-related SAE. One subject died due to an AE of pulmonary embolism during the study; this was deemed unrelated to treatment by the investigator. Twenty-six subjects (19%)

reported at least 1 AE leading to discontinuation. The most common AEs leading to discontinuation of vistusertib (reported in ≥4 subjects overall) were fatigue (7%), nausea (4%), decreased appetite (3%), diarrhea (3%), mucositis (3%), rash (3%), and vomiting (3%).

Although most subjects experienced an AE, the drug was considered to be well tolerated with easily manageable side effects by the investigators. A total of 68 subjects (50%) experienced an AE Grade 3, 1 subject (1%) had a Grade 4 AE, and 1 subject (1%) had a Grade 5 AE (incidence rates include DLTs at non-tolerated doses). Fifteen (12%) subjects on doses below the MTD experienced AEs that led to the discontinuation of vistusertib, and no subjects on a dose below the MTD for the qd continuous and intermittent (2 consecutive days, 2 days on, 5 days off) dosing schedules reported any AEs which led to discontinuation. AEs that defined the drug's nontolerability were generally reversible within a week of stopping treatment with vistusertib. One hundred and five subjects (78%) had a duration of treatment (including periods of dose interruption) of >3 months. One subject had duration of treatment of 18 months.

Combination with fulvestrant (Faslodex®)

At the Study D2270C00005 (Study 5, combination with fulvestrant) MTD doses (continuous and intermittent dosing), the most frequently reported AEs related to vistusertib (reported in ≥15% subjects overall) were fatigue, nausea, rash, diarrhea, decreased appetite, vomiting, hyperglycemia, mucositis, pruritus, headache, anemia, asthenia, dry skin, constipation, dizziness and skin hyperpigmentation. The most frequently reported AEs of Grade ≥3 (reported in >1 subject at an MTD, irrespective of causality) were rash, fatigue, nausea, infections, mucositis, vomiting, anemia, diarrhea, hyperglycemia, and hypophosphatemia.

At the Study D2270C00005 (Study 5, combination with fulvestrant) MTD doses, no SAE Medical Dictionary for Regulatory Activities (MedDRA) term was reported in >1 subject. The SAEs in the continuous dosing groups of 50 mg bid plus fulvestrant and 75 mg qd plus fulvestrant were pulmonary embolism, infections, neutropenia, renal impairment, and spinal compression fracture. The SAEs in the intermittent dosing group of 125 mg bid plus fulvestrant were vomiting, nausea, hypercalcemia, diarrhea, infections, colitis, enteritis and subdural hematoma. Two subjects had related SAEs: 1 subject (75 mg qd) had Grade 4 febrile neutropenia; and 1 subject (125 mg bid) had Grade 3 nausea, Grade

3 vomiting, and Grade 3 diarrhea. All these SAEs were considered by the investigator to be related to vistusertib, but not fulvestrant.

There was one death due to an AE in the Study D2270C00005 (Study 5, combination with fulvestrant) MTD of 75 mg qd + fulvestrant (continuous dosing). This was an AE of sepsis of unknown etiology, which was deemed unrelated to treatment by the investigator.

Although there has been no formal comparison of the safety of vistusertib administered alone or in combination with fulvestrant, the safety profiles appear similar.

Additional clinical safety information for vistusertib in combination with paclitaxel can be found in the Vistusertib Investigator Brochure.

1.3 BENEFIT/RISK

Aberrant activation of mTOR can occur via variety of mechanisms in BCR-driven malignancies, including activation/mutation of PI3K, activation of spleen tyrosine kinase (SYK), PKC or BTK. The evidence that mTOR functions at the convergence of many of the above signaling pathways, provides a solid rationale for the use of mTOR in combination with BTK inhibitors in hematologic diseases.

Agents that target components of the PI3K-AKT-mTOR pathway are under investigation for the treatment of DLBCL (Blum 2015). Given the highly heterogeneous nature of DLBCL, it is not clear whether all subtypes of DLBCL will be susceptible to PI3K inhibitors, or whether inhibition of TORC1 alone will deliver efficacy in this disease. The mTOR inhibitor, everolimus, has shown clinical activity in MCL, DLBCL and high-grade FL (Witzig et al 2005; Witzig et al 2011). Preliminary findings from an ongoing Phase 2 study (CCI [redacted]) evaluating vistusertib monotherapy in DLBCL appear to show acceptable tolerability and activity in GCB and non-GCB subtypes of DLBCL. Ibrutinib monotherapy has shown clinical activity in patients with de novo DLBCL, including patients with GCB subtype of DLBCL showing that the BTK pathway can be active even in patients with GCB subtype (Wilson 2015). Ibrutinib monotherapy has also shown clinical activity in RS, as has acalabrutinib (Ayers & Mato 2016, Hillmen et al 2016).

In nonclinical models of DLBCL, the combination of the BTK inhibitor, ibrutinib, with vistusertib delivered regressions and strong apoptosis induction. In these models, synergistic inhibition of BCR signaling was observed, particularly inhibition of cap-dependent translation and NF-κB/signaling (Ezell et al 2014). Similar results have been

obtained with acalabrutinib in combination with vistusertib (see Section 3.2.1). In summary, there is compelling nonclinical and clinical rationale for exploring the combination of mTOR and BTK inhibition for the treatment of patients with B-cell malignancies.

As of 03 September 2017, acalabrutinib has been administered to over 2000 participants in clinical studies, including subjects with hematologic malignancies, solid tumor, or rheumatoid arthritis, and participants who are healthy volunteers or with mild to moderate hepatic impairment. No SAEs have been reported in the hepatic impairment trial or in the healthy volunteer trials. Acalabrutinib has been administered alone and in combination with other kinase inhibitors, anti-CD20 antibodies, chemoimmunotherapy (eg, bendamustine/rituximab), and an anti-programmed cell death 1 (PD-1) receptor antibody. No DLTs have been identified for acalabrutinib monotherapy or when administered in combination with the aforementioned agents. Current clinical safety data supports combining acalabrutinib with other agents.

As of 05 October 2015, 547 subjects have been enrolled in studies with vistusertib. A total of 465 subjects have received vistusertib alone or in combination with other agents. DLTs reported at nontolerated doses for vistusertib were fatigue, diarrhea, mucositis, nausea, vomiting and rash. Of these AEs, gastrointestinal effects (eg, diarrhea, nausea and vomiting, and rash) are overlapping with observed AEs for acalabrutinib. Therefore, the primary objective of this protocol is to determine the safety of this combination in subjects with relapsed/refractory disease and few therapeutic options. As such, this study includes a formal DLT assessment of subjects dosed with the combination (see Section 3.0). In addition, toxicity management guidelines are provided in this protocol for potential overlapping toxicities and other AEs (see Section 3.9). Lastly, this protocol includes study-stopping guidelines as outline in Section 3.13.

2.0 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE:

Part 1 Primary Objective:

To determine a dose and schedule for vistusertib in combination with acalabrutinib 100 mg bid for evaluation in Part 2

Part 2 Primary Objectives:

To evaluate the safety of acalabrutinib and vistusertib when coadministered

2.2 SECONDARY OBJECTIVES:

- To evaluate the PK of acalabrutinib and vistusertib when coadministered
- To evaluate the clinical activity of acalabrutinib and vistusertib, when coadministered, as measured by ORR, including CR rate, DOR, DRR, PFS and OS

2.3 EXPLORATORY OBJECTIVES:

- CCI

3.0 STUDY DESIGN

This study is a multicenter, open-label, randomized (Part 1 only) parallel group study to be conducted at approximately 15 to 20 sites. The study *was originally designed to be* divided into 2 parts. The Phase 1 portion of the study (Part 1) evaluate*d* the safety, PK, and PD of combining acalabrutinib 100 mg bid and vistusertib (various doses and schedules). Part 1 *was to* be used to select the vistusertib dose and schedule for Phase 2. The Phase 2 portion of the study (Part 2) *was to* allow for expansion groups in select B-cell histologies to further evaluate safety, efficacy, and PKPD of the combination treatment*; however, the Sponsor has decided to close the study prior to initiating Part 2*.

Part 1

Part 1 of the study will include adult subjects with any of the following relapsed/refractory disease types:

- De novo DLBCL
- Transformed DLBCL

- RS

Subjects will take acalabrutinib bid at approximately 12-hour intervals. A treatment cycle is defined as 28 days. The acalabrutinib dose will be 100 mg bid. Acalabrutinib is administered on every day of the 28-day cycle. Eligible subjects will be randomized 1:1 to receive one of the following starting regimens of vistusertib using an IXRS:

Schedule 1 (continuous dosing): Vistusertib 35 mg bid continuous dosing (1 cycle = 28 days), n=6

--Or--

Schedule 2 (intermittent dosing): Vistusertib 100 mg bid intermittent dosing (2 days on/ 5 days off over the 28 day cycle), n=6

The rationale for study design and dose selection is provided in Section 3.2 of this protocol. The study schema is presented in Figure 2.

Although acalabrutinib monotherapy has not demonstrated DLTs to date, the safety of the combination of acalabrutinib and vistusertib in this patient population needs to be assessed. Therefore, a safety analysis (see Section 3.14) will occur when 6 subjects have been enrolled in each schedule. Standard DLT criteria (defined below) will be used to assess safety during the first cycle of treatment of the combination treatment. (To be evaluable for DLT, subjects who have not experienced DLT must have received at least 75% of schedule doses. Subjects who have experienced DLT do not have a minimum dosing requirement.) Each schedule is independently assessed. Escalation to the next dose level of vistusertib cannot occur until the DLT review period has been completed.

If ≤1 DLTs occur during cycle 1 in the 6 subjects enrolled in a given schedule, then the dose of vistusertib will be escalated as outlined below and 6 new subjects will be enrolled and assessed for DLT.

	Level -1 (Starting Dose)	**Target Level**	**Level +1**
Continuous dosing schedule (**Schedule 1**)	35 mg bid (daily) n=6	50 mg bid (daily) n=6	75 mg bid (daily) n=6
Intermittent dosing schedule (**Schedule 2**)	100 mg bid (2 days on/ 5 days off) n=6	125 mg bid (2 days on/ 5 days off) n=6	150 mg bid (2 days on/ 5 days off) n=6

Abbreviations: bid = twice per day
1 cycle = 28 days for vistusertib dosing

If ≥2 DLTs occur during cycle 1 in the 6 subjects enrolled in the continuous dosing schedule at the starting dose, then Schedule 1 will be considered not tolerated and no further enrollment will occur.

If ≥2 DLTs occur during cycle 1 in the 6 subjects enrolled in the intermittent dosing schedule at the starting dose, then 6 additional subjects will be enrolled at 75 mg bid 2 days on / 5 days off (ie, Level -2) and assessed for DLTs. If ≥2 DLTs occur at Level -2 for the intermittent dosing schedule, then Schedule 2 will be considered not tolerated and no further enrollment will occur.

Part 1 will enroll approximately 12 to 36 subjects depending on safety. The safety results (eg, DLTs, discontinuation due to adverse events and tolerability) of Part 1 *were to* be used to select the vistusertib dose/schedule for Part 2. Any DLTs attributed to the combination after cycle 1 *were* also *to* be taken into consideration when determining the vistusertib dose and schedule for Part 2.

Enrollment into Dose Level 1 and beyond (Part 2) was discontinued by the sponsor. The primary reason for discontinuation of Part 2 was that inhibition of the Torc-2 protein, which is a target of vistusertib, was not adequate as determined by PD studies. In addition, PK data from subjects at vistusertib Dose Level 0 suggested that increasing the dose to Level 1 would only increase exposure by approximately 20%, which is not expected to provide sufficient Torc-2 coverage to differentiate from approved Torc-1 inhibitors and could increase risk for toxicity.

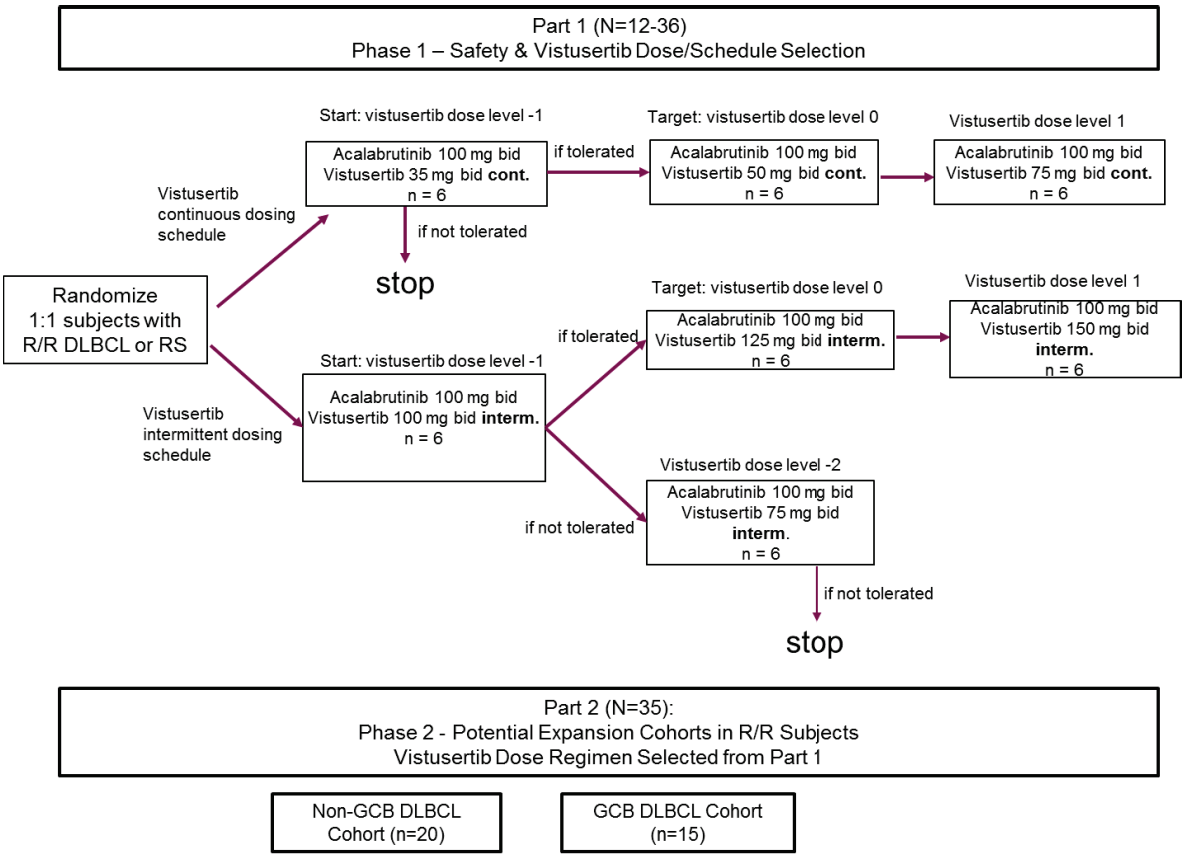
Part 2

Part 2 *was designed to* consist of expansion groups of 15 or 20 subjects per histology (N≤35 total for Part 2) provided the safety results from Part 1 of the study indicate*d* that further evaluation of the combination *was* warranted. *As mentioned above, the study was closed before initiating Part 2.*

Subjects showing clinical benefit (ie, no disease progression) and who are tolerating study treatment may remain on study for up to a total of 12 cycles of treatment. Subjects who have received 12 cycles of treatment (ie, been on study for approximately 12 months) and are deriving clinical benefit from acalabrutinib monotherapy or the combination of acalabrutinib and vistusertib may *remain on study treatment beyond the first 12 months until disease progression occurs or* becomes eligible to enroll in either a rollover study of acalabrutinib monotherapy or a rollover study of the combination of acalabrutinib and vistusertib, respectively.

Refer to Appendix 1 and Appendix 2 for a comprehensive list of study assessments and their timing. The study schema is provided below (Figure 2).

Figure 2. Study Schema



Abbreviations: bid = twice daily; cont. = continuous dosing: DLBCL = diffuse large B-cell lymphoma; GCB = germinal center B-cell; interm. = intermittent dosing; non-GCB = non-germinal center B-cell; R/R = relapsed/refractory; RS = Richter syndrome
Note: On 21 May 2018, a decision was made by the sponsor to stop enrollment and close the study before initiating Dose Level 1 and Part 2.

3.1 STUDY PARAMETERS

3.1.1 Safety Parameters

Type, frequency, severity, and relationship to study drug of any TEAEs or abnormalities of laboratory tests, SAEs, DLTs, or AEs leading to discontinuation of study drug(s).

For consistency of interpretation, AEs and laboratory results will be coded using MedDRA, and the severity of AEs will be graded using the CTCAE, Version *5.0* or higher. Standard definitions for seriousness will be applied (see Section 6.1.2).

3.1.2 Pharmacodynamic, Pharmacokinetic and Biomarker Parameters

The occupancy of BTK by acalabrutinib will be measured in PBMCs with the aid of an acalabrutinib analogue probe. The effect of acalabrutinib and vistusertib on biologic markers of B-cell function will also be evaluated. Cell populations will be monitored for effect of treatment, which may include, but are not limited to, leukocyte or lymphocyte subsets (eg, T, B and NK cells) and their activation states. CCI [redacted]

The following PK parameters will be calculated, whenever possible, from plasma concentrations of acalabrutinib and vistusertib *(Note: These will not be collected or assessed for subjects whose study participation extends past the first 12 cycles.)*:

- $AUC_{0\text{-last}}$: Area under the plasma concentration-time curve calculated using linear trapezoidal summation from time 0 to time last, where "last" is the time of the last measurable concentration
- $AUC_{0\text{-inf}}$: Area under the plasma concentration-time curve from 0 to infinity, calculated using the formula: $AUC_{0\text{-inf}}=AUC_{0\text{-last}} + C_{last} / \lambda_z$, where λ_z is the apparent terminal elimination rate constant (whenever possible)
- C_{max}: Maximum observed plasma concentration
- T_{max}: Time of the maximum plasma concentration (obtained without interpolation)
- $t_{½}$: Terminal elimination half-life
- λ_z: Terminal elimination rate constant
- CL/F: Oral clearance
- V_z/F: Oral volume of distribution

3.1.3 Efficacy Parameters

- ORR (CR + PR)
- DRR
- CR rate
- DOR
- PFS

- OS

Analysis of efficacy parameters is provided in Section 5.5.4. *The efficacy evaluations will not be assessed for subjects whose study participation extends past the first 12 cycles.*

3.2 RATIONALE FOR STUDY DESIGN AND DOSING REGIMEN

3.2.1 Rationale for Combining mTOR and BTK Inhibition

Decades of research across various oncologic diseases support the fact that multidrug regimens (eg, polychemotherapy or chemoimmunotherapy) produce higher and more durable CR rates than single-agent chemotherapy. However, these benefits are often outweighed with the increased toxicity associated with multidrug regimens. The high risk:benefit ratio of multidrug regimens means these regimens are less likely to be used in elderly patients or patients with comorbid conditions. The advent of highly selective, targeted agents to treat B-cell malignancies, such as BCR signaling antagonists, has changed the risk:benefit paradigm traditionally associated with chemotherapy agents. When administered as single agents, they have produced high ORR in some patients with B-cell malignancies. For example, ibrutinib, a small molecule inhibitor of BTK, has been approved for the treatment for CLL/SLL, MCL, MZL and WM. In addition, ibrutinib has shown clinical efficacy in other B-cell malignancies including FL (Advani et al 2012), as well as in de novo (Wilson et al 2015) and transformed DLBCL (specifically RS; Ayers & Mato 2016). Acalabrutinib has also shown clinical activity in CLL and RS (Byrd et al 2016, Hillmen et al 2016) and MCL (Wang et al 2017).

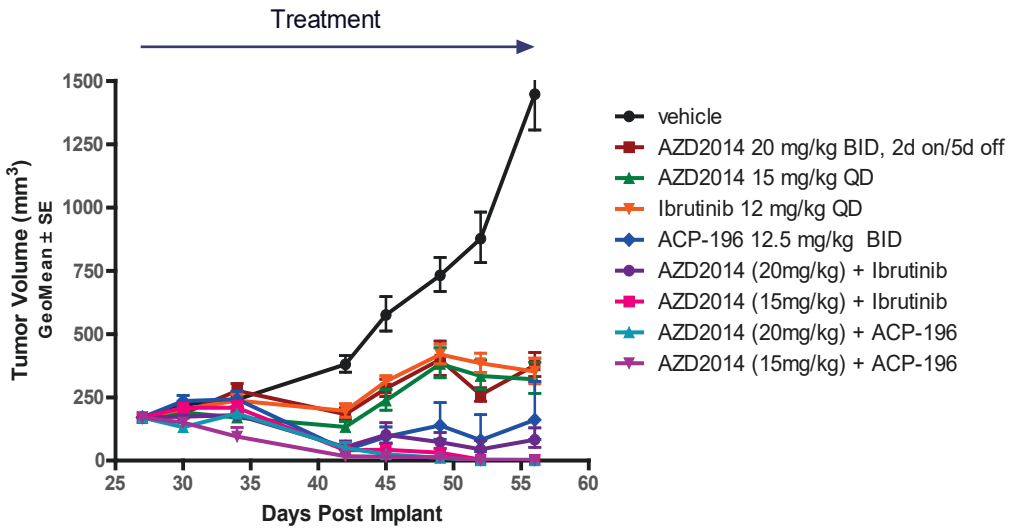
However, the proportion of patients with CRs when treated with BCR signaling antagonists, as monotherapy, is low compared with traditional polychemotherapy or chemoimmunotherapy (Advani et al 2012, Blum 2015). Also, in more aggressive histologies the median DOR can be low (<12 months) (Blum 2015). The question remains whether “targeted combination” therapy can produce more durable responses and potentially more CRs, including MRD negativity, than single agents without an undue associated increase in toxicity.

The mechanism of action of vistusertib (Section 1.2) suggests the potential to combine it with a number of anticancer treatments, including BTK inhibitors. The multiplicity of mechanisms involved in transducing signals from the BCR and the existence of multiple negative feedback loops support the hypothesis that inhibiting BTK signaling together with inhibition of mTORC1/2 may deliver clinical benefit. This theory has been evaluated

preclinically in a non-GLP xenograft model. Briefly, mice (n=10/group) were implanted with OCI-Ly-10 (a DLBCL cell line) and 14 days after tumor implantation were orally gavaged with test articles for 28 days.

Figure 3 shows greater efficacy when combining vistusertib with either ibrutinib or acalabrutinib compared with each agent administered alone.

Figure 3. Tumor Volume Over Time



Abbreviations: ACP-196 = acalabrutinib; AZD2014 = vistusertib; BID = twice per day; d = days; QD = once per day

As is typical of dose-finding studies, Part 1 of this study includes "all comer" patients with relapsed/refractory DLBCL (ie, either de novo or transformed DLBCL, including RS). The expansion portion of the study will enroll only de novo DLBCL and will focus on evaluating the efficacy of combination therapy in GCB (n=15) vs non-GCB (n=20) subtypes. Preliminary findings from an ongoing Phase 2 study (CCI [redacted]) evaluating vistusertib monotherapy in de novo DLBCL appear to show acceptable tolerability and activity in GCB and non-GCB subtypes. In addition, though ibrutinib monotherapy has shown preferential activity in the activated B cell-like (ABC) subtype of DLBCL, a partial response was observed in a patient with GCB subtype and tumor regressions were also seen in 4 additional patients with GCB subtype (Wilson et al 2015)—providing clinical evidence that the BTK pathway is activated in some patients with GCB subtype. Therefore, the purpose of Part 2 *was* to evaluate the combination therapy in both subtypes to determine whether the combination therapy is active across subtypes or shows preferential activity for a particular subtype. *On 21 May 2018, a decision was made by the sponsor to stop enrollment and close this study after*

evaluating the safety, efficacy, PK, and PD of acalabrutinib in combination with vistusertib at Dose Level -1 and Dose Level 0. In general, the acalabrutinib and vistusertib (an mTOR1 and mTOR2 dual inhibitor) combination was well tolerated in subjects with relapsed/refractory DLBCL enrolled in Dose Level -1 and Dose Level 0. However, modest clinical efficacy was observed at both dose levels. Clinical PD biomarker data demonstrated expected acalabrutinib PD but variable vistusertib PD on TORC1 and TORC2 biomarkers as measured in surrogate tissue (ie, lymphocytes). More specifically, the TORC2 biomarker was minimally modulated. PK modeling indicated that increasing dose levels and/or changing dosing schedules would not improve target engagement.

3.2.2 Dose Selection Rationale

As described in Section 1.1.3, acalabrutinib is currently being evaluated in a Phase 1/2 study in subjects with CLL, RS, or prolymphocytic leukemia (CCI [redacted]; Byrd et al 2016). In this study, subjects have received oral dosages of 100 to 400 mg qd and 100 to 200 mg bid of acalabrutinib. All tested dose levels have been well tolerated. No DLT has occurred at any dose level and the MTD was not reached. PD results from this study also show 100 and 200 mg bid have the highest BTK occupancy at 24 hours of all the regimens evaluated. Robust clinical responses have been observed. Acalabrutinib is also being evaluated in Phase 3 studies in subjects with CLL or MCL. The dosage selected for these studies is 100 mg bid based on PD results of the dose escalation study and is, likewise, the dosage selected for this protocol.

Acalabrutinib 100 mg bid has also been evaluated in various indications (ie, B-cell malignancies and solid tumors) alone and in combination with anti-CD20 antibodies, chemotherapy, a PI3K inhibitor, and an anti-PD-1 antibody. No DLTs have been identified for acalabrutinib alone or when given in combination with the aforementioned agents. Therefore, the proposed dosage for this protocol for acalabrutinib is 100 mg bid.

Vistusertib has been evaluated at several doses and schedules. Monotherapy vistusertib 50 mg bid continuous and 125 mg bid 2 days on and 5 days off has been well tolerated. However, to reduce the potential for overlapping toxicities, the vistusertib dosages being evaluated have been reduced to 35 mg bid continuous (Level -1 for continuous dosing schedule) and 100 mg bid 2 days on and 5 days off (Level -1 for intermittent dosing schedule). *Amendment 2 of this protocol added a higher dose level of vistusertib (Level +1) to Part 1 of the protocol. However, as mentioned previously, the*

sponsor stopped the study after evaluating the efficacy, safety, PD, and PK data from the subjects treated with the lower dose levels of vistusertib.

This proof-of-concept study will assess the clinical potential of a dual BTK and mTORC1/2 inhibition approach by evaluating the safety, PK, PD and efficacy of acalabrutinib and vistusertib in relapsed/refractory subsets of B-cell malignancies.

3.3 SELECTION OF STUDY POPULATION

3.3.1 Inclusion Criteria

Eligible subjects will be considered for inclusion in this study if they meet **all** of the following criteria:

1. Diagnosis of relapsed/refractory DLBCL as documented by medical records and with histology based on criteria established by WHO:
    a. If a subject has de novo DLBCL, the diagnosis is confirmed by biopsy and is immunohistologically characterized as de novo non-GCB DLBCL or de novo GCB DLBCL. Note that PMBCL is excluded from this protocol. **Tumor tissue must also be available for sending to the sponsor for central cell of origin testing.**
    b. If the subjects has RS, the diagnosis is confirmed by biopsy and is immunohistologically characterized as transformation to DLBCL. **Tumor tissue must also be available for sending to the sponsor for central pathology testing. This histology applies to Part 1 only.**
    c. If the subjects has transformed DLBCL, the diagnosis is confirmed by biopsy and is immunohistologically characterized as transformation to DLBCL from indolent lymphoma (eg, follicular lymphoma). **Tumor tissue must also be available for sending to the sponsor for central pathology testing. This histology applies to Part 1 only.**
2. Men and women ≥18 years of age.
3. Prior treatment for lymphoid malignancy:
    a. If the subject has DLBCL, there is no curative option with conventional therapy and the prior treatment included ≥ 1 prior combination chemoimmunotherapy regimen (eg, anthracycline based therapy with rituximab such R-CHOP). Also subjects should have relapsed after ASCT or should be noncandidates for ASCT.
    b. If the subject has RS, the subject must have had ≥1 prior treatment with a combination chemoimmunotherapy regimen.
4. Presence of radiographically measurable lymphadenopathy or extranodal lymphoid malignancy (defined as the presence of a ≥1.5 cm lesion, as measured in the longest dimension by CT scan for all histologies).
5. Documented active disease that is relapsed or refractory defined as:
    a. Relapse: disease progression after completion of the treatment regimen preceding entry into the study.
    b. Refractory: progressive disease or stable disease as best response at any point during chemotherapy (>4 cycles of first-line or 2 cycles of later-

line therapy) or relapsed at ≤12 months from autologous stem cell transplantation (Crump et al 2017).

6. ECOG performance status of ≤2.
7. Adequate hematologic function, independent of transfusion and growth factor support for ≥14 days before screening, defined as:
    a. ANC >1000 cells/mm^3 (1.0 x 10^9/L)
    b. Platelet count >75,000 cells/mm^3 (75 x 10^9/L) or >50,000 cells/mm^3 with bone marrow involvement
    c. Hemoglobin >8.0 g/dL
8. Adequate hepatic and renal function at screening defined as:
    a. Serum AST and ALT ≤2.5 x ULN if no demonstrable liver involvement or ≤3 x ULN in the presence of liver metastases
    b. Bilirubin ≤1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin)
    c. Serum creatinine ≤1.5 times ULN and creatinine clearance >30 mL/min (measured or calculated by Cockcroft and Gault equation [(140-Age) • Mass (kg)/(72 • creatinine mg/dL) • multiply by 0.85 if female])
9. PT/INR <1.5 x ULN and aPTT <1.5 x ULN.
10. Serum potassium within normal range.
11. Women should be using adequate contraceptive measures, should not be breast feeding and must have a negative pregnancy test before start of dosing if of child-bearing potential or must have evidence of nonchildbearing potential by fulfilling one of the following criteria at screening:
    a. Postmenopausal women, defined as either women aged >50 years and amenorrheic for ≥12 months following cessation of all exogenous hormonal treatments, or, women under 50 years old who have been amenorrheic for ≥12 months following the cessation of exogenous hormonal treatments, and have serum FSH and LH levels in the postmenopausal range for the institution.
    b. Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation.
    c. Medically confirmed, irreversible premature ovarian failure.

    Women who are sexually active and of childbearing potential must be willing to use 2 forms of contraception (see Section 3.11.7) from the time of screening to 90 days after discontinuing study drug(s).
12. Men *who are sexually active must* use barrier contraception (ie, condoms) *in addition to the highly effective contraception* and refrain from sperm donation during the study and *until 2* days after *the subject's last dose of acalabrutinib or 16 weeks after the subject's last dose of vistusertib, whichever is longer*. If not done previously, storage of sperm before receiving vistusertib will be advised to male subjects with a desire to have children.
13. Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules/tablets without difficulty.
14. Willing to follow sunlight protection measures while taking vistusertib (eg, using sunscreen and avoiding excessive sun exposure) and for 90 days after the last dose of vistusertib.

15. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local patient privacy regulations).

Host genetics research study (optional):

For inclusion in the optional genetic component of the study, subjects must fulfil the following additional criteria:

16. Provision of signed, written, and dated informed consent for genetic research. If a subject declines to participate in the genetic component of the study, there will be no penalty or loss of benefit to the subject. The subject will not be excluded from other aspects of the study described in this protocol, so long as they consented to the main study.
17. Whole blood transfusion given within 120 days of genetic sample collection should be leukocyte depleted.

Tumor biopsy study (optional):

For inclusion in the optional tumor biopsy component of the study, subjects must fulfil the following additional criteria:

18. Provision of signed, written, and dated informed consent for fresh lymph node tumor biopsies (at baseline, on study and at progression). If a subject declines to participate in the tumor biopsy component of the study, there will be no penalty or loss of benefit to the subject. The subject will not be excluded from other aspects of the study described in this protocol, so long as they consented to the main study.
19. Presence of superficial lymphadenopathy for the lymph node biopsy.

3.3.2 Exclusion Criteria

Subjects will be ineligible for this study if they meet **any** of the following criteria:

1. History of prior malignancy except for the following:
   a) Malignancy treated with curative intent and with no evidence of active disease present for more than 2 years before screening and felt to be at low risk for recurrence by treating physician.
   b) Adequately treated lentigo maligna melanoma without current evidence of disease or adequately controlled nonmelanomatous skin cancer.
   c) Adequately treated carcinoma in situ without current evidence of disease.
2. As judged by the Investigator, any evidence of severe or uncontrolled systemic disease (eg, severe hepatic impairment, interstitial lung disease [bilateral, diffuse, parenchymal lung disease]), or current unstable or uncompensated respiratory or cardiac conditions, or uncontrolled hypertension, history of, or active, bleeding diatheses (eg, hemophilia or von Willebrand disease) or uncontrolled active systemic fungal, bacterial, viral, or other infection (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment), or intravenous anti-infective treatment within 2 weeks before first dose of study drug.
3. Diagnosis of PMBCL.
4. Known history of infection with HIV.
5. Serologic status reflecting active hepatitis B or C infection.

   a) Subjects who are anti-HBc positive and who are surface antigen negative will need to have a negative PCR result before enrollment. Those who are hepatitis B surface antigen positive or hepatitis B PCR positive will be excluded.
   b) Subjects who are hepatitis C antibody positive will need to have a negative PCR result before enrollment. Those who are hepatitis C PCR positive will be excluded.
6. Active CMV infection (positive CMV IgM and/or positive PCR result)
7. Undergone any of the following procedures or experienced any of the following conditions currently or in the preceding 6 months:
   a) coronary artery bypass graft
   b) angioplasty
   c) vascular stent
   d) myocardial infarction
   e) angina pectoris
   f) congestive heart failure (NYHA Grade ≥2)
   g) ventricular arrhythmias requiring continuous therapy
   h) supraventricular arrhythmias, including atrial fibrillation, which are uncontrolled
   i) hemorrhagic or thrombotic stroke, including transient ischemic attacks or any other central nervous system bleeding.
8. Current refractory nausea and vomiting, malabsorption syndrome, disease significantly affecting GI function, resection of the stomach, extensive small bowel resection that is likely to affect absorption, symptomatic inflammatory bowel disease, partial or complete bowel obstruction, or gastric restrictions and bariatric surgery, such as gastric bypass.
9. History of CNS lymphoma, leptomeningeal disease or spinal cord compression.
10. History of severe allergic or anaphylactic reactions to kinase inhibitors or history of hypersensitivity to active or inactive excipients of vistusertib or acalabrutinib or drugs with a similar chemical structure or class to vistusertib or acalabrutinib.
11. Presence of a GI ulcer diagnosed by endoscopy within 3 months before screening.
12. Uncontrolled Type 1 or Type 2 diabetes mellitus (eg, hemoglobin A1c ≥7%).
13. Any clinically significant pre-existing severe renal disease (eg, glomerulonephritis, nephritic syndrome, Fanconi Syndrome or renal tubular acidosis) or high risk of developing severe renal impairment.
14. Major surgical procedure within 28 days before first dose of study drug. Note: If a subject had major surgery, they must have recovered adequately from any toxicity and/or complications from the intervention before the first dose of study drug.
15. Unresolved toxicities from prior anticancer therapy, defined as having not resolved to CTCAE, Version *5.0* Grade 0 or 1, or to the levels dictated in the inclusion/exclusion criteria, with the exception of alopecia.
16. Any hematopoietic growth factors (eg, filgrastim [G-CSF], sargramostin [GM-CSF]) within 7 days of the first dose of study drug or pegylated G-CSF (pegfilgrastim) or darbepoetin within 14 days of the first dose of study drug.
17. Vaccinated with live, attenuated vaccines within 4 weeks of first dose of study drug.
18. Abnormal ECHO or MUGA at baseline (LVEF <40% and shortening fraction SF <15%). Appropriate correction to be used, if a MUGA is performed.

19. Mean resting QTc calculated using Fridericia's formula (QTcF) >450 msec obtained from 3 ECGs; family or personal history of long or short QT syndrome; Brugada syndrome or known history of QTc prolongation or torsade de pointes within 12 months of the subject entering the study.
20. Factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, or family history of sudden unexplained death under 40 years of age. Concomitant medications known to prolong QTc should be used with caution and cannot be used during the first 28 days on study.
21. Any therapeutic antibody within 4 weeks of first dose of study drugs.
22. Prior use of standard antilymphoma therapy or radiation therapy within 14 days of receiving the first dose of study drug (not including palliative radiotherapy). Subjects must have recovered from acute toxicity due to prior treatment. Note: Subjects previously treated with BTK, mTOR or PI3K inhibitors are not excluded from this protocol; however, the 14-day washout and recovery from acute toxicity from these agents still applies.
23. Ongoing immunosuppressive therapy, including systemic (eg, intravenous or oral) corticosteroids for treatment of lymphoid cancer or other conditions. Note: Subjects may use topical or inhaled corticosteroids or low-dose steroids (≤ 10 mg of prednisone or equivalent per day) as therapy for comorbid conditions. During study participation, subjects may also receive systemic corticosteroids as needed for treatment-emergent comorbid conditions.
24. Exposure to strong or moderate inhibitors or inducers of CYP3A4/5, P-gp, or BCRP, if taken within the stated washout periods before the first dose of study drug (see Appendix 4).
25. Exposure to specific substrates of the drug transporters OATP1B1, OATP1B3, MATE1 and MATE2K within the appropriate washout period for each drug (a minimum of 5 x reported elimination half-life) before the first dose of study drug (see Appendix 4).
26. Requires or receiving therapeutic anticoagulants, with the exception of short-acting heparins, within 7 days of first dose of study drug.
27. Requires treatment with proton-pump inhibitors (eg, 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.
28. Recent history (past 12 months) of drug abuse or alcohol abuse, as judged by the investigator.
29. Concurrent participation in another therapeutic clinical trial.

3.3.3 Replacement of Subjects

Subjects will not be replaced in this study unless needed to meet the requirement of 6 subjects for DLT review as described in Section 3.0.

3.3.4 Enrollment and Randomization Procedures

Enrollment of a subject into the study will be performed according to the following procedure:

- The study center will notify the sponsor when a clinically eligible subject is identified and is ready to screen, to ensure enrollment availability on the study.
- After the subject has signed and dated the Informed Consent Form (ICF), all screening procedures have been completed, and eligibility has been confirmed, the subject can be officially enrolled into the study.
- To confirm eligibility, the study center will fax/email a completed Enrollment Confirmation Form to the sponsor. The enrollment date will be the date that the sponsor confirms enrollment.
- The sponsor will aim to fax/email a completed Enrollment Confirmation Form to the study center within 48 to 72 hours of receipt.
- Treatment assignment for Part 1 only will occur through the use of an IXRS. As subjects qualify for enrollment, designated study center personnel will contact the IXRS, which will assign a treatment arm to each eligible subject.

Treatment must begin within the screening window (see Appendix 1) and, for Part 1 only, after the site has received the treatment allocation per IXRS.

3.4 STUDY DRUG

3.4.1 Premedications

No specific premedications or supporting medications are required in conjunction with acalabrutinib or vistusertib administration.

3.4.2 Formulation, Packaging, and Storage

Acalabrutinib and vistusertib are manufactured according to cGMP regulations and will be provided to the investigational site by Acerta Pharma or designee. Study drug should be stored according to the instructions on the label affixed to the package of the drug product.

If a drug shipment arrives damaged, or if there are any other drug complaints, a Product Complaint Form should be completed and emailed or faxed to the sponsor or the sponsor's representative. Refer to the Acalabrutinib Investigator Brochure and Vistusertib Investigator Brochure for additional information regarding the drug products to be used in this trial.

3.4.3 Administration of Study Drug

Investigators are prohibited from supplying study drug to any subjects not properly enrolled in this study. The investigator must ensure that subjects receive study drug only from personnel who fully understand the procedures for administering the drug.

Acalabrutinib and vistusertib are intended to be administered orally twice daily with 8 ounces (approximately 240 mL) of water (avoid grapefruit juice or Seville orange juice due to potential inhibition of CYP3A). Study drugs can be administered without regard to food. Doses should be administered 12 hours apart (a window of ±1 hour is allowed) at approximately the same times each day. If subjects are enrolled in Level -1 (intermittent dosing for vistusertib), then vistusertib will be taken bid for 2 days followed by 5 days of drug holiday (no vistusertib dosing) before starting again with 2 days of dosing.

The acalabrutinib capsules and vistusertib tablets should be taken concomitantly and should be swallowed intact. Subjects should not attempt to open capsules/break or crush tablets or dissolve in water. If vomiting occurs after taking study drug(s), the subject should not retake study drug(s) until the next scheduled dose.

For either drug, if a dose is not taken within the allowed window, it can be taken up to 2 hours after the scheduled time with a return to the normal schedule the same or following day. If it has been >2 hours, the dose should not be taken and the subject should take the next dose at the next scheduled time. The missed dose will not be made up and must be returned to the site at the next scheduled visit. If a subject needs to take a dose earlier than scheduled, the subject can take the dose up to 2 hours earlier than the scheduled time. Subjects should make every reasonable effort to take the study drug(s) on time.

Guidance on co-administration of acalabrutinib with agents that affect gastric pH is provided in Section 3.11.5.

3.4.4 Assuring Subject Compliance

For treatments that are taken in the clinic, subjects should take the dose from the drug dispensed for them for that particular time period. All other study drug treatments will be taken at home. Subjects will receive a drug diary to record the specific time each dose was taken and to record reasons for any missed doses.

Subject compliance with acalabrutinib/vistusertib dosing will be assessed at every visit and recorded in the electronic data capture (EDC) system. The subject will be instructed to bring the diary and any remaining capsules/tablets to the clinic at their next visit. The study staff will review the diary and ask the subject if all of the capsules/tablets were administered. Any remaining or returned capsules/tablets will be counted and recorded as described in Section 7.6. Returned capsules/tablets must not be redispensed to another subject.

3.5 STUDY TREATMENT SCHEDULE

Acalabrutinib 100 mg will be administered twice daily every day of the 28-day cycle. The following doses and schedules of vistusertib are being evaluated in this protocol:

Vistusertib Dose Levels and Schedules				
	Dose Level	**Schedule Type**	**Dose Schedule**	**Weekly Dose**
SCHEDULE 1	Starting dose (Level -1)	Continuous	35 mg twice daily continuous	490 mg
	Target dose (Level 0)	Continuous	50 mg twice daily continuous	700 mg
SCHEDULE 2	Level -2 dose	Intermittent	75 mg twice daily 2 days on/5 days off	300 mg
	Starting dose (Level -1)	Intermittent	100 mg twice daily 2 days on/5 days off	400 mg
	Target dose (Level 0)	Intermittent	125 mg twice daily 2 days on/5 days off	500 mg

Note: 1 cycle is 28 days.

To initiate a new cycle of therapy with vistusertib, the subject must have an ANC ≥1,000/μL and a platelet count ≥50,000/μL and no drug-related nonhematologic Grade ≥3 toxicity on day 1 of each cycle. If these criteria are not met, vistusertib may be held for a maximum of 28 days to allow for retreatment. Treatment may only be restarted once the results of repeat assessments indicate that these criteria have been met.

Refer to Section 3.8 for information on dose delays and modifications.

3.6 DURATION OF THERAPY

Treatment with acalabrutinib and vistusertib, in Part 1, may be continued until disease progression or an unacceptable drug-related toxicity occurs as defined in the protocol.

Subjects who do not tolerate vistusertib may continue to receive acalabrutinib monotherapy provided they are deriving clinical benefit.

Subjects showing clinical benefit and who are tolerating study treatment may remain on study for up to 12 cycles of treatment. Subjects who have received 12 cycles of treatment (ie, been on study for approximately 12 months) and are deriving clinical benefit from acalabrutinib monotherapy or the combination of acalabrutinib and vistusertib may *remain on study treatment beyond the first 12 months until disease progression occurs or* becomes eligible to enroll in either a rollover study of acalabrutinib monotherapy or a rollover study of the combination of acalabrutinib and vistusertib, respectively.

The end of study for this protocol is when the last subject on the study has either discontinued the study or been transitioned to a rollover protocol.

3.7 ASSESSMENT OF DOSE-LIMITING TOXICITY (DLT)

For Part 1, a DLT will be defined as the occurrence of any of the following AEs (Note that all AEs of the specified grades should be recorded as DLTs with the exception of those that are clearly, and incontrovertibly, due to extraneous causes such as disease progression):

1. Any Grade ≥3 nonhematologic toxicity except Grade 3 nausea, vomiting, or diarrhea that respond to supportive therapy (eg, improvement by 1 or more severity grade within 48 hours).
2. Any of the following hematologic toxicities:
    a. Grade 4 neutrophil count decrease lasting >7 days, despite growth factor support.
    b. Grade 4 platelet count decrease or Grade 3 platelet count decrease with bleeding.
    c. Grade ≥3 febrile neutropenia.
    d. Grade 4 anemia, unexplained by underlying disease.
3. Clinical TLS (defined in Table 3) that occurs despite protocol-recommended management will be considered a DLT.
4. Laboratory TLS (defined in Table 4) will be considered a DLT if the metabolic abnormalities do not resolve within 72 hours despite protocol-required management.
5. Dosing delay due to toxicity for >28 consecutive days.

A DLT excludes:

1. Alopecia of any grade
2. Isolated laboratory changes of any grade without clinical sequelae or clinical significance

Table 3. Howard definition of clinical tumor lysis syndrome

The presence of laboratory TLS and one or more of the following criteria:
1. Acute kidney injury[a] defined as creatinine increase in serum creatinine level of 0.3 mg/dL (26.5 µmol/L) or the presence of oliguria, defined as average urine output of <0.5 mL/kg/hr for 6 hours (or a single value >1.5 times the upper limit of the age-appropriate normal range if no baseline creatinine measurement is available) 2. Cardiac dysrhythmia or sudden death probably or definitely caused by hyperkalaemia 3. Cardiac dysrhythmia, sudden death, seizure, neuromuscular irritability (tetany, paresthesias, muscle twitching, carpopedal spasm, Trousseau's sign, Chvostek's sign, laryngospasm or bronchospasm), hypotension, or heart failure probably or definitely caused by hypocalcaemia[b]

Abbreviations: hr = hour; TLS = tumor lysis syndrome; ULN = upper limit of normal
a. By definition, if acute kidney injury is present, the patient has clinical TLS.
b. Not directly attributable to a therapeutic agent.
Modified from Howard et al 2011

Table 4. Howard definition of laboratory tumor lysis syndrome

Uric acid	>476 µmol/L (>8.0 mg/dL)
Potassium	>6.0 mmol/L (>6.0 mEq/L)
Phosphorous	>1.5 mmol/L (>4.5 mg/dL)
Corrected calcium	<1.75 mmol/L (<7.0 mg/dL) or ionized calcium <1.12 (0.3 mmol/L)[a]

Laboratory tumor lysis syndrome is the presence of 2 or more electrolyte changes above or below the thresholds described above occurring during the same 24-hour period within 3 days before the start of therapy or 7 days afterward. This assessment assumes that a subject has or will receive adequate hydration (±alkalinisation) and a hypouricemic agent(s).
a. The corrected calcium level in milligrams per decilitre is the measured calcium in milligrams per decilitre +(0.8 x [4-albumin in grams per decilitre])
Modified from Howard et al 2011

3.8 DOSING DELAYS AND MODIFICATIONS

Substantial acute toxicities should be managed as medically indicated and with temporary suspension of study drug(s), as appropriate. Dose reductions or holds and initiation of supportive care are allowed as clinically indicated by the treating physician. In general, for each subject, a maximum of 2 dose reductions will be allowed; however, exceptions from this rule may be discussed with the medical monitor on a case-by-case basis.

Possible dose reduction options for vistusertib are presented in Table 5. If a subject's vistusertib dose is reduced, then dose re-escalation of vistusertib is not permitted.

However, for subjects receiving lower doses of vistusertib at study entry, they may be escalated to higher doses when the higher dose levels clear DLT review. These intrapatient escalations from the dose at study entry will occur on a case-by-case basis with input from the Medical Monitor. Any changes to the dosing regimen must be recorded on the appropriate electronic case report form (eCRF).

Table 5. Vistusertib dose reduction options

Starting dose	1st dose reduction	2nd dose reduction	3rd dose reduction[a]
35 mg	25 mg	discontinue	not applicable
50 mg	35 mg	25 mg	discontinue
75 mg	50 mg	25 mg	discontinue
100 mg	75 mg	50 mg	25 mg
125 mg	100 mg	75 mg	50 mg

a. If allowed after consultation with medical monitor

To initiate a new cycle of therapy with vistusertib, the subject must have an ANC ≥1,000/μL and a platelet count ≥50,000/μL and no drug-related nonhematologic Grade ≥3 toxicity on day 1 of each cycle. If these criteria are not met, vistusertib may be held for a maximum of 28 days to allow for retreatment. Treatment may only be restarted once the results of repeat assessments indicate that these criteria have been met.

Table 6 provides dose reduction options for acalabrutinib.

Table 6. Acalabrutinib dose reduction options

Starting dose	1st dose reduction	2nd dose reduction
100 mg bid	100 mg qd	Discontinue

Note: Temporary withholding of acalabrutinib for as little as 7 days can cause a transient worsening of disease and/or of constitutional symptoms. Transient worsening of disease during temporary interruption of study therapy (eg, for drug-related toxicity, surgery, or intercurrent illness) may not indicate disease progression. In such circumstances, and if medically appropriate, following discussion with the medical monitor, subjects may resume therapy and relevant clinical, laboratory, and/or radiologic assessments should be done to document whether tumor control can be maintained or whether actual disease progression has occurred.

If acalabrutinib is reduced for apparent treatment-related toxicity, the dose need not be re-escalated, even if there is minimal or no toxicity with the reduced dose. However, if the subject tolerates a reduced dose of acalabrutinib for ≥4 weeks then the dose may be increased to the next higher dose level, at the discretion of the investigator. Such re-escalation may be particularly warranted if further evaluation reveals that the AE that led to the dose reduction was not treatment related. Any changes to the dosing regimen must be recorded on the appropriate eCRF.

Dose reduction and discontinuation guidelines for hematologic and nonhematologic toxicities are shown below in Table 7 and Table 8, respectively.

In general, if a subject experiences a Grade 1 or Grade 2 hematologic or nonhematologic toxicity, no dose modification is required.

If a subject experiences a Grade 3 or Grade 4 toxicity, not attributable to the disease or disease-related processes under investigation, dosing will be interrupted and/or the dose reduced (see Table 7 and Table 8) and supportive therapy administered as required.

If the toxicity resolves or reverts to CTCAE Grade ≤2 within 28 days and the subject was showing clinical benefit, treatment with study drug(s) may be restarted.

If the toxicity does not resolve to CTCAE Grade ≤2 within 28 days, then the subject should be withdrawn from the study and observed until resolution of the toxicity. Maximal drug holiday allowed is 28 consecutive days.

3.8.1 Dose modifications for hematologic toxicities

Please refer to Table 7 for dose modifications due to hematologic toxicities. The number of dose reduction levels available for vistusertib and acalabrutinib will vary depending on the starting dose as described above.

If the table indicates that the vistusertib dose should be reduced and the subject is already on the lowest dose available for vistusertib as per Table 5, vistusertib should be discontinued. If the table indicates that the acalabrutinib dose should be reduced and the subject is already on 100 mg/day (see Table 6), acalabrutinib should be discontinued. If vistusertib is discontinued, acalabrutinib monotherapy can continue on this protocol (Appendix 2). However, vistusertib monotherapy cannot continue if acalabrutinib is discontinued.

Table 7. Dose modifications for hematologic toxicities

NCI CTCAE Grade	Acalabrutinib Action	Vistusertib Action
Febrile neutropenia Grade 3 or 4	Withhold **acalabrutinib** and **vistusertib** until infection is resolved, antibiotics no longer required and ANC Grade ≤2 or baseline	
	acalabrutinib restart with 1 level dose reduction or discontinue (see Table 6)	**vistusertib** restart with 1 level dose reduction or discontinue (see Table 5)
2nd episode of **febrile neutropenia** Grade 3 or 4	Withhold **acalabrutinib** and **vistusertib** until infection is resolved, antibiotics no longer required and ANC Grade ≤2 or baseline	
	acalabrutinib restart with 1 level dose reduction or discontinue (see Table 6)	**vistusertib** restart with 1 level dose reduction or discontinue (see Table 5)
3rd episode of **febrile neutropenia** Grade 3 or 4	Discontinue **acalabrutinib** and **vistusertib**	
Neutrophil count decrease Grade 4 lasting >7 days despite growth factor support	Withhold **acalabrutinib** and **vistusertib** until Grade ≤2 or baseline	
	acalabrutinib restart at the same dose level	**vistusertib** restart with 1 level dose reduction or discontinue (see Table 5)
2nd episode of **neutrophil count decrease** Grade 4 lasting >7 days despite growth factor support	Withhold **acalabrutinib** and **vistusertib** until Grade ≤2 or baseline	
	acalabrutinib restart with 1 level dose reduction or discontinue (see Table 6)	**vistusertib** restart with 1 level dose reduction or discontinue (see Table 5)
3rd episode of **neutrophil count decrease** Grade 4 lasting >7 days despite growth factor support	Discontinue **acalabrutinib** and **vistusertib**	
Platelet count decrease, Grade 4 without bleeding requiring blood or platelet transfusion	Withhold **acalabrutinib** and **vistusertib** until Grade ≤2 or baseline	
	acalabrutinib restart at the same dose level	**vistusertib** restart with 1 level dose reduction or discontinue (see Table 5)
2nd episode of **platelet count decrease**, Grade 4 without bleeding requiring blood or platelet transfusion	Withhold **acalabrutinib** and **vistusertib** until Grade ≤2 or baseline	
	acalabrutinib restart with 1 level dose reduction or discontinue (see Table 6)	**vistusertib** restart with 1 level dose reduction or discontinue (see Table 5)

NCI CTCAE Grade	Acalabrutinib Action	Vistusertib Action
3rd episode of **platelet count decrease**, Grade 4 without bleeding requiring blood or platelet transfusion	Discontinue **acalabrutinib** and **vistusertib**	
Platelet count decrease, Grade 3 or 4 **with bleeding** requiring blood or platelet transfusion	Withhold **acalabrutinib** and **vistusertib** until Grade ≤2 or baseline	
	acalabrutinib restart with 1 level dose reduction or discontinue (see Table 6)	**vistusertib** restart with 1 level dose reduction or discontinue (see Table 5)
2nd episode of **platelet count decrease**, Grade 3 or 4 **with bleeding** requiring blood or platelet transfusion	Discontinue **acalabrutinib** and **vistusertib**	

Abbreviations: ANC = absolute neutrophil count; CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute

3.8.2 Dose modifications for nonhematologic toxicities

In case of Grade 4 treatment-related nonhematologic toxicity, discontinue acalabrutinib and vistusertib.

Grade 3 toxicities require dose modifications, temporary treatment interruptions or discontinuation of vistusertib and acalabrutinib.

Please refer to Table 8 for dose modifications due to Grade 3 nonhematologic toxicities. The number of dose reduction levels available for vistusertib and acalabrutinib will vary depending on the starting dose.

Table 8. Dose modification guidance in the event of Grade 3 nonhematologic toxicities except liver dysfunction*

Occurrence	Acalabrutinib Action	Vistusertib Action
First	Withhold **acalabrutinib** and **vistusertib** until recovery to Grade ≤2 or baseline	
	acalabrutinib restart at the same dose	**vistusertib** restart with 1 level dose reduction or discontinue (see Table 5)
Second	Withhold **acalabrutinib** and **vistusertib** until recovery to Grade ≤2 or baseline	
	acalabrutinib restart with 1 level dose reduction or discontinue (see Table 6)	**vistusertib** restart with 1 level dose reduction or discontinue (see Table 5)
Third	Withhold **acalabrutinib** and **vistusertib** until recovery to Grade ≤2 or baseline	
	acalabrutinib restart with 1 level dose reduction or discontinue (see Table 6)	**vistusertib** restart with 1 level dose reduction or discontinue (see Table 5)

*For guidance on liver toxicity refer to Section 3.9.12 and Appendix 5.

3.9 MANAGEMENT OF TOXICITES

This section provides recommendations for treatment of potential toxicities associated with vistusertib, acalabrutinib or the combination of vistusertib and acalabrutinib and guidance about modifying the doses of acalabrutinib and vistusertib due to those toxicities.

Generally, Grade 1 or 2 nonhematologic and/or hematologic toxicities do not require vistusertib or acalabrutinib dose reductions and should be managed as medically indicated (with or without short dose interruptions) by the treating physician.

Grade 3 and 4 toxicities require dose modifications, temporary treatment interruptions or discontinuation of vistusertib and acalabrutinib. These are described in Section 3.8.1 for hematologic and Section 3.8.2 for nonhematologic toxicities.

3.9.1 Recommendations for Evaluation and Treatment of Severe Fatigue

Severe fatigue is an identified risk for vistusertib. Subjects should be advised of the potential for severe fatigue associated with vistusertib use. If Grade ≥3 fatigue occurs,

the dosing should be held for ≤14 days before being restarted at a lower dose (Section 3.8.2).

Routine clinical work-up to exclude reasons other than the underlying disease and/or vistusertib treatment may be performed, including laboratory analyses to rule out anemia, metabolic (acidosis, hyperglycemia) or hormonal (adrenal or thyroid) problems, infections, or cardiac problems.

3.9.2 Recommendations for Treatment of Diarrhea

Diarrhea is an overlapping risk for vistusertib and acalabrutinib. Subjects should be made aware of the risk of diarrhea while receiving treatment with vistusertib and acalabrutinib. Subjects should be advised to drink sufficient fluids and have a supply of loperamide available throughout treatment. However, loperamide should not be administered prophylactically.

As soon as the first liquid stool occurs, subjects should start treatment with loperamide immediately and take electrolyte-containing fluids. Subjects should inform their study doctor.

The recommended antidiarrheal treatment is loperamide, to be administered as per package information and usual clinical practice. Loperamide should not be administered for more than 48 consecutive hours.

Hospitalization is recommended for management of diarrhea under the following circumstances:

- Diarrhea associated with fever
- Diarrhea requiring intravenous hydration
- Diarrhea persisting beyond 48 hours after the initiation of high-dose loperamide therapy.

Please refer to Section 3.8.2 for dose modifications required for Grade ≥3 diarrhea.

3.9.3 Recommendations for the Treatment of Nausea and Vomiting

Nausea and vomiting are overlapping risks for acalabrutinib and vistusertib. Subjects should be made aware of the risk of nausea/vomiting while receiving treatment with vistusertib and acalabrutinib. Not all subjects require antiemetics, and therefore they should not receive antiemetics prophylactically. However, once a subject has experienced nausea and vomiting, serotonin (5-HT3) antagonists should be administered on subsequent dosing days, eg, dolasetron 100 mg by mouth daily, granisetron 2 mg by mouth daily or 1 mg by mouth bid.

Please see National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Antiemesis 2016 (NCCN 2016) for further information.

Aprepitant should not be used as it is a moderate CYP3A4/5 inhibitor (Appendix 4).

Please refer to Section 3.8.2 for dose modifications required for Grade ≥3 nausea and/or vomiting.

If nausea and vomiting are not being managed with the regimen above, start a breakthrough treatment with the addition of 1 agent of a different drug class, for example:

- dexamethasone 8 mg PO at day 1 of the vistusertib dosing period or
- metoclopramide 10 to 40 mg PO or
- olanzapine 5 to 10 mg PO or
- promethazine (Phenergan)12.5 to 25 mg every 6 hours

on the vistusertib dosing days before the vistusertib dose.

If this is still not managing the nausea and vomiting sufficiently, add lorazepam 0.5 to 2 mg by mouth or sublingually every 4 to 6 hours as needed, but only on the vistusertib dosing days.

Should upper abdominal pain develop, an H2 blocker can be added. See Section 3.11.5 regarding guidance on concomitant administration of acalabrutinib and H2 blockers.

3.9.4 Recommendations for Treatment of Decreased Appetite

Decreased appetite should be treated according to local clinical practice. Dietary review is recommended.

3.9.5 Recommendations for Treatment of Rash/Skin Toxicity

Rash/skin toxicity is an overlapping risk for vistusertib and acalabrutinib. Subjects should be made aware of the risk of rash/skin toxicity while receiving treatment with vistusertib and acalabrutinib. Early identification and intervention is critical for the optimal management of rash. Preliminary clinical evidence suggests that antihistaminergic drugs may ameliorate occurrence/severity of rash. Therefore, subjects who develop Grade 1 or 2 changes in their skin condition should be treated with the investigator's choice of antihistaminergic drugs, over the counter moisturizing cream or

ointment, local antihistamines and/or topical or systemic steroids. If bacterial infection is suspected, local and/or systemic antibiotics may be added.

For Grade 3 rash, topical and/or systemic steroids with or without topical and/or systemic antibiotics (to be considered if bacterial infection is suspected) are indicated, together with dose modifications as described in Section 3.8.2; short courses (≤14 days) of corticosteroid treatment at doses that do not exceed 100 mg per day of prednisone or equivalent may be given.

Some example treatments are listed below:

- topical steroids: triamcinolone acetonide 0.025%; desonide 0.05%; fluticasone propionate 0.05%, aclometasone 0.05%
- topical antipruritics: pramoxine 1%; doxepin 5% cream
- oral antihistamines: loratidine, cetirizine, fexofenadine; diphenhydramine 25 to 50 mg every 8 hours; hydroxyzine 25 mg every 8 hours
- topical antibiotics: clindamycin 1-2%; erythromycin 1-2%; metronidazole 1%; silver sulphadiazine1%
- oral antibiotics: doxycycline 100 mg bid; minocycline 100 mg bid; oxytetracycline 500 mg

3.9.6 Recommendations for treatment of Stomatitis/Oral Mucositis/Mouth Ulcers

Stomatitis/oral mucositis/mouth ulcers are identified risks for vistusertib. Subjects should be advised of the potential for stomatitis/oral mucositis/mouth ulcers associated with vistusertib use. For mild toxicity (Grade 1), use conservative measures such as nonalcoholic mouth wash or salt water (0.9%) mouth wash several times immediately after drug administration (1 to 3 hours) and during the day as required until resolution.

For more severe toxicity (Grade 2 or 3), the suggested treatments are topical analgesic mouth treatments (ie, local anesthetics such as benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenolic compounds), with or without topical corticosteroids, such as triamcinolone oral paste 0.1% (eg, Kenalog in Orabase®) or alcohol-free 0.5 to 2 mg/5 mL dexamethasone oral solution (ie, for example Dexsol® or PMS dexamethasone 0.5 mg/5 mL elixir). The mouth rinse will be self-administered at a daily dose of 10 mL three times per day. Most importantly, subjects must be instructed to swish and expectorate the mouth rinse to avoid systemic exposure to dexamethasone.

For further information, please refer to published guidelines (Seiler et al 2014).

For Grade 3 stomatitis/oral mucositis/mouth ulcers, systemic painkillers are indicated (eg, oral or subcutaneous morphine) and dose modification as described in Section 3.8.2.

Vistusertib should be stopped until stomatitis improves to Grade ≤1, and then resumed without a dose reduction. If Grade 2 to 3 stomatitis recurs, dose reduce vistusertib.

Agents containing hydrogen peroxide, iodine, and thyme derivatives may worsen mouth ulcers. It is preferable to avoid these agents.

3.9.7 Recommendations for Treatment of Hyperglycemia

Hyperglycemia may occur with vistusertib use. Subjects should be made aware of this potential risk. Management of hyperglycemia should be performed according to local standards at the discretion of the Investigator. Due to the predicted short half-life of vistusertib, only a short period of hyperglycemia with insulin resistance might be expected. Therefore, early treatment with insulin and/or oral anti-diabetes medication should be carefully evaluated and blood sugars and hypokalemia monitored as per standard clinical practice. If blood glucose levels are <250 mg/dL (Grade 2), generally no medical treatment is required. Dietary modification may be initiated.

For Grade ≥3 hyperglycemia, dose modifications are required (see Section 3.8.2).

3.9.8 Recommendations for Evaluation and Treatment of Electrolyte Changes Including Hypokalemia and Hypophosphatemia

Vistusertib, like other mTOR inhibitors, inhibits pump mechanisms in renal tubules, leading to hypokalemia and hypophosphatemia in a small proportion of subjects. The presence of biochemical abnormalities should be monitored as per the protocol and electrolyte abnormalities should be corrected using oral supplements. The investigator should also consider whether other medication the subject may be receiving, such as diuretics, might have contributed to these abnormalities.

3.9.9 Recommendations for Evaluation and Treatment of Interstitial Lung Disease

A baseline thorax CT scan must be available for all subjects treated with vistusertib, for retrospective analysis and comparison with a high resolution CT scan, should it be required, if symptoms occur during study conduct. Should a subject experience any new respiratory symptoms including cough, dyspnea, lower respiratory tract infections not clearly explained by other factors such as disease progression or anemia, a high

resolution CT scan and pulmonary function tests should be performed, including 3 forced expiratory volumes, forced vital capacity, and carbon monoxide diffusing capacity (DLCO% & DLCO). A recent hemoglobin measurement should also be available at the time of the DLCO evaluation. If these investigations are suggestive of pneumonitis or interstitial lung disease and causality with the study drug cannot be excluded, treatment should be interrupted. In more severe cases treatment with corticosteroids should be considered as per reference Willemsen et al 2016.

3.9.10 Recommendations for Evaluation and Management of Electrocardiogram (ECG) Changes

Subjects who develop persistent, confirmed T-wave repolarization abnormalities (inversion or flattening) on regularly scheduled ECGs should be referred for a cardiology opinion and undergo a follow-up LVEF measurement using the same technology to that used at baseline. As a summary, the following should be evaluated from baseline throughout the study; ECGs should be reported with immediate reference to all previous ECGs to allow trends to be identified without delay.

- ECG and troponin monitoring:
  - screening
  - Cycle 1 Day 1, 15, 22
  - Cycle 2 to 6 Day 1
  - 30-day SFU visit
- Left ventricular (LV) function assessment:
  - screening
  - approximately 2 weeks after a new T-wave inversion or flattening is first recorded (and as clinically indicated)
  - 30-day follow-up visit

3.9.11 Recommendations for Evaluation and Treatment of Renal Effects

Renal effects have been classified as a potential risk for vistusertib and, in animal studies, administration of acalabrutinib at high doses was associated with reversible findings in the kidney (details provided in respective Investigator Brochure). However, no clinically significant renal findings were reported at any dose of vistusertib or acalabrutinib so far.

This study protocol excludes subjects with any clinically significant pre-existing severe renal disease (eg, glomerulonephritis, nephritic syndrome, Fanconi Syndrome or renal tubular acidosis) or high risk of developing severe renal impairment (Section 3.3.2,

Exclusion Criteria #13). Adequate renal function for inclusion at screening is defined in Section 3.3.1 Inclusion Criteria #8.

If Grade ≥3 renal dysfunction develops while the subject is on study, follow dose modification advice shown in Section 3.8.2.

3.9.12 Recommendations for Evaluation and Treatment of Liver Function Test Abnormalities (Risk for Vistusertib and/or Acalabrutinib)

Acalabrutinib and vistusertib are metabolized in the liver, and transaminase elevations are a potential risk for both study drugs. Subjects should be made aware of the risk of possible overlapping toxicities of transaminase elevations while receiving both drugs. Evidence of abnormal liver function should be monitored as per the protocol guidelines. Increased levels of AST, ALT, or serum bilirubin should trigger an investigation of the cause, which may include viral infection or disease progression with liver infiltration. The Investigator should consider whether the abnormal liver function meets the criteria for expedited reporting (see Appendix 5: Actions required in case of increases in liver biochemistry and evaluation of Hy's law).

Vistusertib is metabolized in the liver. For subjects who develop mild liver impairment while on study (Child-Pugh Class A), the recommended dose for vistusertib is 2 dose levels lower than the starting dose, see Table 5. If a dose 2 levels lower than the starting dose is not available, vistusertib should be discontinued. Subjects who develop moderate or severe hepatic impairment (Child-Pugh Class B or C) must hold study drug until resolved to mild impairment (Child-Pugh Class A) or better and will be re-treated at 2 dose levels lower than the starting dose for vistusertib (or discontinue if applicable), see Table 5. Refer the current Acalabrutinib Investigator Brochure for information on administering acalabrutinib to subjects with mild or moderate hepatic impairment.

For guidance on treating liver toxicity, please refer to Table 9 of this protocol.

Table 9. Recommendations for acalabrutinib and vistusertib dose modifications for abnormal liver function results

NCI CTCAE Grade	Recommendation	
	Acalabrutinib	**Vistusertib**
Elevations in ALT, AST, or bilirubin		
Grade 1 (ALT/AST ≤3 x ULN) (Bilirubin ≤1.5 x ULN)	Maintain current dose level and schedule. Monitor ALT, AST, ALP, and bilirubin at least 1x per week.	Maintain current dose level and schedule. Monitor ALT, AST, ALP, and bilirubin at least 1x per week.
Grade 2 (ALT/AST >3-5 x ULN) (Bilirubin >1.5- ≤3 x ULN)	Withhold or continue acalabrutinib (at investigator discretion, after discussion with the medical monitor). Monitor ALT, AST, ALP, and bilirubin at least 1x per week. After 7 days if hepatic enzymes appear to be improving and acalabrutinib was withheld, restart acalabrutinib at current dose level (to prevent disease progression, monitor disease parameters closely). Also, see Appendix 5 for further guidance and actions if the subject meets Potential Hy's law criteria.	Withhold vistusertib. Monitor ALT, AST, ALP, and bilirubin at least 1x per week until all abnormalities have returned to Grade ≤ 1. Administer corticosteroids (initial dose of 0.5 to 1 mg/kg/day prednisone [≥40 mg] or equivalent followed by taper); when all abnormalities have returned to Grade ≤ 1, recommend tapering steroids over no less than 4 weeks. Once abnormalities have returned to Grade ≤ 1, vistusertib may resume at a lower dose level (if applicable, see Table 5). Also, see Appendix 5 for further guidance and actions if the subject meets Potential Hy's law criteria.
Grade 3 (ALT/AST >5-20 x ULN) (Bilirubin >3-10 x ULN)	See recommendations for Grades 2 Also, see Appendix 5 for further guidance and actions if the subject meets Potential Hy's law criteria.	Discontinue vistusertib permanently. Also, see Appendix 5 for further guidance and actions if the subject meets Potential Hy's law criteria.
Grade 4 (ALT/AST >20 x ULN) (Bilirubin >10 x ULN)	Discontinue acalabrutinib permanently. Also, see Appendix 5 for further guidance and actions if the subject meets Potential Hy's law criteria.	Discontinue vistusertib permanently. Also, see Appendix 5 for further guidance and actions if the subject meets Potential Hy's law criteria.

3.9.13 Recommendations for Evaluation and Treatment of Infections

Subjects receiving treatment with vistusertib or acalabrutinib may be at an increased risk of infection. Subjects should be made aware of the risk of possible overlapping risk of infections elevations while receiving both drugs. This should be managed as per clinical practice. In case of Grade 3 infections, the guidelines provided in Section 3.8.2 should be followed.

3.9.14 Recommendations for Other Nonhematologic Toxicities

Other toxicities should be managed as per clinical practice. In case of Grade 3 toxicity, the guidelines provided in Section 3.8.2 should be followed.

Acalabrutinib and vistusertib must be discontinued in case of Grade 4 treatment-related nonhematologic toxicity.

3.9.15 Recommendations for Treatment of Hematologic Findings and Associated Dose Modifications

Cytopenia could be an overlapping toxicity for acalabrutinib and vistusertib. In the presence of CTCAE Grade 3/4 neutropenia/leucopenia/thrombocytopenia/anemia, subject's blood counts should be monitored, using local laboratories, at least twice weekly until recovery.

Please refer to Table 7 for dose modifications due to hematologic toxicities. The number of dose reduction levels available for vistusertib and acalabrutinib will vary depending on the starting dose (Section 3.8).

If the table indicates that the vistusertib dose should be reduced and the subject is already on the lowest dose available for vistusertib as per Table 5, vistusertib should be discontinued. If the table indicates that the acalabrutinib dose should be reduced and the subject is already on 100 mg/day (see Table 6), acalabrutinib should be discontinued.

3.9.16 Recommendations for Tumor Lysis Syndrome (TLS)

TLS is a potential risk for the combination of vistusertib and acalabrutinib. TLS prophylaxis will be at investigator discretion following institutional guidelines. Table 10 provides recommended TLS prophylaxis, which should be followed in addition to institutional guidelines.

Clinical or laboratory TLS (defined in Table 3 and Table 4) may trigger dose modification in accordance with guidelines provided in Section 3.8.2.

Table 10. Recommended TLS prophylaxis based on risk

Type of Cancer	Risk		
	High	**Intermediate**	**Low**
NHL	Burkitt lymphoblastic, B-ALL OR Any LN ≥10 cm	DLBCL/Richter syndrome OR Any LN 5 cm to <10 cm	Indolent NHL
AML/MDS	WBC ≥50,000, monoblastic	WBC 10,000-50,000	WBC ≤10,000
CLL/ALL	Any LN ≥10 cm OR ALC ≥25 x10^9/L AND any LN ≥5 cm	Any LN 5 cm to <10 cm OR ALC ≥25 x10^9/L	All LN <5 cm AND ALC <25 x10^9/L
Multiple myeloma		Rapid proliferation with expected rapid response to therapy	Remainder of patients
	Recommended Prophylaxis		
Hydration[a]	Oral (1.5-2L) and intravenous (150-200 mL/hr as tolerated)	Oral (1.5-2 L) and consider additional intravenous	Oral (1.5-2 L)
Antihyperuricemics	Allopurinol[b]; consider rasburicase if baseline uric acid is elevated	Allopurinol[b]	Allopurinol[b]

Abbreviations: ALC = absolute lymphocyte count; ALL = acute lymphocytic leukemia; AML = acute myeloid leukemia, B-ALL = Burkitt acute lymphoblastic leukemia; CLL = chronic lymphocytic leukemia; DLBCL = diffuse large B-cell lymphoma; hr = hour; LN = lymph node; MDS = myelodysplastic syndrome; NHL = nonHodgkin lymphoma; WBC = white blood cell count

a. Administer intravenous hydration for any patient who cannot tolerate oral hydration.

b. Start allopurinol or xanthine oxidase inhibitor 2 to 3 days before initiation of both study drugs.

Modified from Coiffier et al 2008.

TLS Monitoring

Monitoring for TLS includes checking blood urea nitrogen (BUN), creatinine, phosphate/phosphorus, uric acid, calcium, potassium and lactate dehydrogenase (LDH) levels at least every 6 hours (or more frequently as clinically indicated) in patients at high risk for TLS and as required per institutional standards. Fluid balance must be monitored per institutional standards.

3.10 CONCOMITANT THERAPY

3.10.1 Permitted Concomitant Therapy

Supportive medications in accordance with standard practice (such as for emesis, diarrhea, and nausea; see also Section 3.9.2 and Section 3.9.3) are permitted. Use of granulocyte growth factors (filgrastim and pegfilgrastim) or red blood cell growth factors (erythropoietin) is permitted per institutional policy and in accordance with the American Society of Clinical Oncology guidelines (Smith et al 2015). Please note that treatment with concomitant/prophylactic hematopoietic growth factors should only be considered

during vistusertib drug interruptions, but may be given concomitantly with acalabrutinib. Blood and platelet transfusions may be given in accordance with institutional policy.

For subjects considered at risk for tumor lysis syndrome (see also Section 3.9.16): Administer appropriate hydration and allopurinol or rasburicase per institutional standards before initiating treatment.

For subjects at risk for pneumonitis based on prior history or comorbid conditions: In selected subjects (eg, those with a history of recurrent pneumonias), anti-infectious prevention should be considered. Initiation of antibiotic prophylaxis against pneumocystis infection (eg, with trimethoprim-sulfamethoxazole, dapsone, aerosolized pentamidine, or atovaquone) beginning before study drug administration may be warranted. Such support may also offer the benefit of reducing the risk for other bacterial infections (Stern et al 2014). Prophylaxis with intravenous immunoglobulins (Ig) may be appropriate in subjects with low Ig levels (Raanani et al 2009). Local practices or guidelines regarding infection prophylaxis may be followed.

For infections (see also Section 3.9.13): Bacterial/viral/fungal prophylaxis is allowed per institutional standards**.** Per the protocol, blood counts are monitored at least every 2 weeks for the first 6 cycles of treatment. However, in subjects with ANC <1000 cells/mm^3, blood counts should be monitored weekly or more frequently as clinically indicated. Subjects with active CMV infection are excluded from the trial. However, should a subject acquire CMV infection during treatment, then the subject should be discontinued from treatment and treated for CMV appropriately.

3.10.2 Prohibited or Restricted Concomitant Therapy

Any chemotherapy, anticancer immunotherapy, corticosteroids (at dosages equivalent to prednisone >20 mg/day), therapeutic anticoagulants (with the exception of short-acting heparins), experimental therapy, and radiotherapy are prohibited.

At study entry, subjects may be using topical or inhaled corticosteroids or low-dose steroids (≤10 mg of prednisone or equivalent per day) as therapy for comorbid conditions, but use of corticosteroids as therapy of the lymphoid cancer is not permitted. During study participation, subjects may also receive corticosteroids at any required dosage as needed for treatment-emergent adverse events (for example see Section 3.9).

Live vaccines within 30 days before the first dose of trial treatment and while participating in the trial are prohibited. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

Concomitant medications known to prolong QT should be used with caution and cannot be used during the first 28 days on study. The following website (or a similar site) should be consulted to search for drugs with QT prolongation potential:

https://crediblemeds.org

Refer to Section 3.11.5 for guidance/restrictions on drugs that may cause drug-drug interactions.

3.11 PRECAUTIONS

3.11.1 Hepatitis B Reactivation

Serious or life-threatening reactivation of viral hepatitis may occur in subjects treated with a BTK inhibitor (De Jésus Ngoma et al 2015). Therefore, subjects who are anti-HBc positive, or have a known history of HBV infection, should be monitored monthly with a quantitative PCR test for HBV DNA. Monthly monitoring should continue until 12 months after last dose of acalabrutinib. Any subject with a rising viral load (above lower limit of detection) should discontinue acalabrutinib and have antiviral therapy instituted and a consultation with a physician with expertise in managing hepatitis B. Insufficient data exist regarding the safety of resuming acalabrutinib in subjects who develop HBV reactivation.

3.11.2 Progressive multifocal leukoencephalopathy (PML)

Cases of PML have been reported in subjects treated with acalabrutinib.

Signs and symptoms of PML may cognitive and behavioral changes, language disturbances, visual disturbances, sensory deficits, weakness, and coordination and gait difficulties

If PML is suspected, hold further treatment with acalabrutinib treatment until PML is excluded. A diagnostic evaluation may include (but is not limited to):

- Neurologic consultation

- Brain magnetic resonance imaging (MRI)
- PCR analysis for John Cunningham (JC) virus DNA in cerebrospinal fluid

If PML is confirmed, permanently discontinue acalabrutinib.

3.11.3 Phototoxicity

Phototoxicity has been classified as a potential risk for vistusertib; however, there have been no relevant clinical findings so far. Subjects should be advised of the need for sunlight protection measures such as use of sunscreen and wearing of sunglasses during administration of vistusertib. Use of sun beds and tanning booths should be avoided. These measures should be adopted for a period of 3 months after receiving their final dose of vistusertib.

3.11.4 Dietary Restrictions

Acalabrutinib and vistusertib can be taken with or without food. Because acalabrutinib and vistusertib are metabolized by CYP3A, subjects should be strongly cautioned against consumption of grapefruit, grapefruit juice, or Seville orange juice (which contain potent CYP3A inhibitors) or using herbal remedies or dietary supplements (in particular, St John's wort, which is a potent CYP3A inducer).

Otherwise, subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

3.11.5 Drug-drug Interactions

Acalabrutinib

The effect of agents that reduce gastric acidity (antacids or proton pump inhibitors) on acalabrutinib absorption was evaluated in a healthy volunteer study (ACE HV 004). Results from this study indicate that subjects should avoid the use of calcium carbonate containing drugs or supplements for a period of at least 2 hours before and at least 2 hours after taking acalabrutinib. Use of omeprazole, esomeprazole, lansoprazole or any other proton pump inhibitors while taking ACP-196 is not recommended due to a potential decrease in study drug exposure. However, the decision to treat with proton-pump inhibitors during the study is at the investigator's discretion, with an understanding of the potential benefit to the subject's gastrointestinal condition and a potential risk of decreased exposure to acalabrutinib. Although the effect of H2-receptor antagonists (such as famotidine or ranitidine) on acalabrutinib absorption has not been evaluated, if

treatment with an H2-receptor antagonist is required, the H2-receptor antagonist should be taken approximately 2 hours after an acalabrutinib dose.

Acalabrutinib is not a strong direct inhibitor or inducer or CYP isoforms; thus, acalabrutinib, at the currently used clinical doses, is unlikely to be a perpetrator of a drug-drug interaction at the level of inhibition or induction of CYP isoforms. Acalabrutinib is partially metabolized by CYP3A; its exposure is affected when coadministered with strong CYP3A inducers or inhibitors. Consequently, the concomitant use of strong inhibitors/inducers of CYP3A (see Appendix 4) should be avoided when possible. If co-administration of moderate or strong CYP3A inhibitors is required when a subject is receiving acalabrutinib, monitor for potential toxicity.

Vistusertib

Drug interactions have been classified as an important potential risk for vistusertib.

While subjects may not enter the study if they have taken (within the appropriate washout period for each drug before the first dose of study treatment) any of the CYP3A4/5, P-gp, or BCRP inhibitors or inducers detailed in Appendix 4, it could be possible to allow their short-term administration during the study under the following circumstances:

- If a subject requires short-term administration of a restricted CYP3A4/5, P-gp, or BCRP inhibitor, vistusertib treatment must be withheld 3 days before the first dose and not restarted until at least the concomitant therapy has been discontinued for the appropriate washout period described in Appendix 4.
- If a subject requires short-term administration of a restricted CYP3A4/5, P-gp, or BCRP inducer, this should be clearly documented in the eCRF and may then be permitted, but this could lead to lower levels of vistusertib and a potential reduction in clinical efficacy.
- If a subject requires short-term administration of restricted substrates of OATP1B1, OATP1B3, MATE1 or MATE2K transporters, vistusertib treatment must be withheld for 3 days before the first dose and not restarted until the concomitant therapy has been discontinued for the appropriate washout period described in Appendix 4 and until at least after the end of Cycle 1.

The lists of CYP and transporter inhibitors/inducers and transporter substrates are not exhaustive and the absence of a drug from these lists does not imply that its

combination with vistusertib is safe. Investigators should discuss with the Medical Monitor before initiating treatment with concomitant medications that might pose drug interactions with vistusertib.

Information on any treatment in the 4 weeks before starting study drug(s) and all concomitant treatments given during the study with reasons for the treatments should be recorded. If medically feasible, subjects taking regular medication, with the exception of those excluded from this study (ie, substrates of OATP1B1, OATP1B3, MATE1 and MATE2K drug transporters), should be maintained on it throughout the study period.

3.11.6 Surgery

Susceptibility to bleeding has been observed with ibrutinib (IMBRUVICA® prescribing information). As a precaution, it is suggested that acalabrutinib be withheld for 3 days before and 3 days after any major surgical procedure.

3.11.7 Reproductive Toxicity

Reproductive toxicity has been classified as an important potential risk for vistusertib. It is not currently known whether vistusertib affects fertility in humans. If not done previously, storage of sperm/eggs before receiving vistusertib will be advised to male/female subjects with a desire to have children. Results from studies of acalabrutinib on fertility and embryofetal development are provided in the Acalabrutinib Investigator Brochure.

Definition of contraception:

Highly effective methods of contraception (to be used during heterosexual activity) are defined as methods that can achieve a failure rate of <1% per year when used consistently and correctly. Such methods include the following:

- *Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, which may be oral, intravaginal, or transdermal*
- *Progestogen-only hormonal contraception associated with inhibition of ovulation, which may be oral, injectable, or implantable*
- *Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)*
- *Bilateral tubal occlusion*

- *Vasectomy of a female subject's male partner (with medical assessment and confirmation of vasectomy surgical success)*
- *Sexual abstinence (only if refraining from heterosexual intercourse during the entire period of risk associated with the study treatments)*

Hormonal contraception may be susceptible to interaction with study or other drugs, which may reduce the efficacy of the contraception method.

Abstinence (relative to heterosexual activity) can only be used as the sole method of contraception if it is consistently employed during the entire period of risk associated with the study treatments as the subject's preferred and usual lifestyle. Periodic abstinence (eg, calendar, ovulation, sympto-thermal, and post-ovulation methods) and withdrawal are not acceptable methods of contraception.

If a contraceptive method is restricted by local regulations/guidelines, then it does not qualify as an acceptable highly effective method of contraception for subjects participating at sites in the relevant country/region.

Women who are sexually active and of childbearing potential must use the contraceptive methods described above from the time of screening to 90 days after discontinuing study drug(s).

Men *who have a partner who is a woman* of childbearing potential *must use highly effective contraception with the additional* use *of a condom* during the study and for *16 weeks after the subject's last dose of vistusertib*. Male subjects should refrain from donating sperm from the start of dosing until *16 weeks* after the *subject's last dose of vistusertib*. If male subjects wish to father children*,* they should be advised to arrange for freezing of sperm samples before receiving the first dose of *vistusertib*.

Subjects should promptly notify the investigator if they or their partners become pregnant during this study or within *2* days after their last dose of *acalabrutinib or 16 weeks after the subject's last dose of vistusertib, whichever is longer*. If a woman becomes pregnant during the treatment period, she must discontinue acalabrutinib and vistusertib. Pregnancy must be reported as outlined in Section 6.2.3.

3.11.8 Overdose Instructions

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the highest dose being studied. An overdose or incorrect administration of study drug is not an AE unless it results in untoward medical effects.

Any study drug overdose or incorrect administration of study drug should be noted on the appropriate eCRF.

All AEs associated with an overdose or incorrect administration of study drug should be recorded on the eCRF. If the associated AE fulfills serious criteria, the event should be reported to the sponsor immediately (ie, no more than 24 hours after learning of the event).

For any subject experiencing an acalabrutinib overdose, observation for any symptomatic side effects should be instituted, and vital signs, biochemical and hematologic parameters should be followed closely (consistent with the protocol or more frequently, as needed). Appropriate supportive management to mitigate adverse effects should be initiated. If the overdose ingestion of acalabrutinib is recent and substantial, and if there are no medical contraindications, use of gastric lavage or induction of emesis may be considered.

A dose of vistusertib in excess of the highest dose specified according to the protocol will constitute an overdose. There is currently no known antidote to vistusertib, and the treatment of overdose should be supportive for the underlying symptoms. To date, no subject has experienced an overdose with vistusertib that was associated with AEs.

3.12 WITHDRAWAL OF SUBJECTS FROM STUDY TREATMENT

The investigator, in consultation with the medical monitor, may withdraw any subject from study treatment, if, in the investigator's opinion, it is not in the subject's best interest to continue.

Any subject has the right to withdraw from the study at any time. In addition, subjects may be withdrawn from study treatment for the following reasons:

- Progressive disease
- Completed treatment
- Start of alternative anticancer therapy
- Adverse event
- Pregnancy
- Investigator decision
- Subject's withdrawal of consent from study
- Decision by sponsor to terminate the study
- Subject lost to follow-up

- Death
- Other

3.13 REASONS FOR STUDY EXIT/TERMINATION

Reasons for study exit include:

- Subject's withdrawal of consent from study
- Decision by sponsor to terminate the study
- Subject lost to follow-up
- Death

In case a subject is lost to follow-up, every possible effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation. The measures taken to follow up must be documented.

When a subject withdraws before completing the study, the reason for withdrawal must be documented in the eCRF and in the source documents. Subjects who withdraw consent should still be encouraged to complete the SFU assessments before withdrawing consent, but these assessments cannot be mandated once consent is withdrawn. Subjects who are withdrawn or removed from study treatment will not be replaced.

The sponsor may decide to prematurely terminate the study at any time. Potential reasons for terminating the study include:

- Inadequate enrollment
- Undue safety risk (eg, drug-related deaths or toxicities leading to study drug discontinuation)
- Lack of efficacy (eg, low response rate or low durability of response)

3.14 DATA AND SAFETY MONITORING

This trial will be monitored in accordance with the sponsor's pharmacovigilance procedures. AEs and SAEs will be reviewed internally as part of ongoing safety surveillance. Quarterly conference calls with the investigators and applicable site staff will be conducted to discuss study progress, obtain investigator feedback and exchange, and discuss "significant safety events" (ie, DLTs, AEs leading to dose reductions or discontinuation, related SAEs, and deaths). In addition, for the DLT review, mandatory safety teleconferences will occur before any vistusertib dose escalation can occur and

before the expansion phase of the protocol can open. The DLT review meeting(s) will require the attendance of the investigators (or delegated subinvestigators) and the sponsor medical monitor and biostatistician. The expansion phase of the protocol will not open unless a tolerated dose and schedule for vistusertib has been identified in Part 1.

4.0 STUDY ACTIVITIES AND ASSESSMENTS

The schedule of events is provided in Appendix 1 for combination treatment and in Appendix 2 for acalabrutinib monotherapy. Descriptions of the scheduled evaluations are outlined below and complete information on study drug and dosing is provided in Section 3.4.

Before study entry, throughout the study, and at the follow-up evaluation, various clinical and diagnostic laboratory evaluations are outlined. The purpose of obtaining these detailed measurements is to ensure adequate safety and tolerability assessments. Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated. This study will primarily use central laboratory testing for safety laboratory evaluations.

4.1 DESCRIPTION OF PROCEDURES

4.1.1 Informed Consent

The subject must read, understand and sign the ICF approved by the IRB/IEC, confirming his or her willingness to participate in this study before initiating any screening activity that is not considered standard of care by institutional standards. Subjects must also grant permission to use protected health information, if required by local regulations. This protocol also has optional DNA and tumor tissue sampling procedures that subjects may elect to participate in through the consent process.

4.1.2 Confirmation of Eligibility

Subject eligibility for enrollment will be assessed per Section 3.3. All screening procedures, unless otherwise indicated, should be completed within 30 days of the first dose of study drug(s).

4.1.3 Medical History

Collect and record the subject's complete history through review of medical records and by interview. Concurrent medical signs and symptoms must be documented to establish

baseline severities. A disease history, including the date of initial diagnosis and list of all prior anticancer treatments, and responses and duration of response to these treatments, also will be recorded.

4.1.4 Adverse Events

The accepted regulatory definition for an AE is provided in Section 6.1. The AE reporting period is described in Section 6.2.1. Important additional requirements for reporting SAEs are explained in Section 6.2.

4.1.5 Concomitant Medications and Therapy

Document all concomitant medications and procedures from the start of screening procedures through the survival follow-up period.

4.1.6 ECOG Performance Status

The ECOG performance index is provided in Appendix 3.

4.1.7 Cumulative Illness Rating Scale-Geriatric (CIRS-G)

CIRS-G (Appendix 7) is an indicator of illness severity and comorbidity in older subjects (Extermann et al 1998). CIRS-G scoring is to be performed by a licensed provider (eg, physician, physician assistant, or nurse) for all subjects.

Rating Strategy

Please see specific scoring guidelines below for each organ system.

0: No Problem.

1: Current mild problem or past significant problem.

2: Moderate disability or morbidity/requires “first line” therapy.

3: Severe/constant significant disability/”uncontrollable” chronic problems.

4: Extremely severe/immediate treatment required/end organ failure/severe impairment of function.

4.1.8 Physical Examination, Vital Signs, Height & Weight

The screening physical examination will include, at a minimum, the general appearance of the subject, height (screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, nervous system, and lymphatic system.

Symptom-directed physical exams will be done during the treatment period and at the SFU visits.

Vital signs (blood pressure, pulse, oxygen saturation and body temperature) will be assessed after the subject has rested in the sitting position for at least 5 minutes.

4.1.9 Electrocardiogram

Subjects should be in supine position and resting for at least 10 minutes before any study-related ECGs.

Triplicate ECGs are required at screening and Cycle 6 only, or if clinically indicated, at all other visits, single ECGs are required. If an unscheduled ECG is done at any time, then an electrolyte panel (ie, calcium, magnesium, and potassium) must be done to coincide with the ECG testing.

4.1.10 ECHO/MUGA

In addition to screening, an ECHO should be done 14 days after an abnormal ECG finding (T wave inversion/flattening), or when clinically indicated. If an ECHO cannot be taken, a MUGA scan to assess LVEF will be done. In case of any T wave abnormality, the ECHO (or MUGA) should be repeated at the SFU visit to address the question of recovery, during the off-treatment period. Note: An ECHO is preferred over MUGA to avoid unnecessary radiation exposure to subjects.

4.1.11 CT Scan of Thorax

A baseline thorax CT scan must be available for all subjects treated with vistusertib, for retrospective analysis and comparison with a high-resolution CT scan, should it be required, should symptoms of interstitial lung disease occur during study conduct. Note: A separate scan of only the thorax is not required for subjects who have baseline CT scans for tumor assessments per Section 4.3.

4.1.12 Hematology

Hematology studies must include complete blood count (CBC) with differential including, but not limited to white blood cell count, hemoglobin, hematocrit, platelet count, ANC, and absolute lymphocyte count (ALC).

4.1.13 Serum Chemistry

Chemistry will include albumin, alkaline phosphatase, ALT, AST, bicarbonate, BUN, calcium, chloride, cholesterol, C-peptide, creatinine, glucose, LDH, magnesium,

phosphate/phosphorus, potassium, sodium, triglycerides, total bilirubin, total protein, and uric acid for subjects on combination treatment. Cholesterol, C-peptide and triglyceride testing not required for subjects who have discontinued vistusertib and are only receiving acalabrutinib.

If an unscheduled ECG is done at any time, then an electrolyte panel (ie, calcium, magnesium, and potassium) must be done to coincide with the ECG testing.

4.1.14 Pregnancy Testing

Pregnancy testing is required in women of childbearing potential.

4.1.15 Cardiac Troponin

Cardiac troponin testing will be done per the schedule in Appendix 1.

4.1.16 Coagulation

Coagulation studies must include PT, INR and aPTT.

4.1.17 Hepatitis B and C Testing

Hepatitis serology testing must include hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), anti-HBc, and HCV antibody. In addition, any subjects testing positive for any hepatitis serology must have PCR testing during screening and on study (see Appendix 1 and exclusion criterion #5).

Subjects who are anti-HBc positive should have quantitative PCR testing for HBV DNA performed during screening and monthly thereafter. Monthly monitoring should continue until 12 months after last dose of study drug(s). Any subject with a rising viral load (above lower limit of detection) should discontinue study drug and have antiviral therapy instituted and a consultation with a physician with expertise in managing hepatitis B. As IVIG may cause false positive hepatitis serology, monthly PCR testing is not required in subjects who are currently receiving or received prophylactic IVIG within 3 months before study enrollment and have a documented negative anti-HBc test before the initiation of IVIG therapy. PCR testing should be performed when clinically indicated (eg, in the setting of rising transaminase levels).

Subjects with a known history of hepatitis C or who are hepatitis C antibody positive should be tested for HCV RNA performed during screening and at Cycle 6. No further testing beyond Cycle 6 is necessary if PCR results are negative.

Refer to Section 3.11.1, Appendix 1, and Appendix 2 regarding monitoring of subjects who are anti-HBc positive or hepatitis C antibody positive or who have a known history of HBV or HCV.

4.1.18 CMV Testing

CMV testing at screening must include serology testing for CMV IgG, CMV IgM, and CMV PCR testing.

4.1.19 Urinalysis

Urinalysis includes pH, ketones, specific gravity, bilirubin, protein, blood, and glucose.

4.1.20 T/B/NK Cell Count

Flow cytometry testing of peripheral blood will include $CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$ and $CD16/56^+$ cells.

4.1.21 Serum Immunoglobulin

Serum immunoglobulin testing will include IgG, IgM, and IgA.

4.1.22 Pharmacokinetics

Vistusertib PK blood sampling (2 mL per sample) will be collected at predose and at approximately 1, 2, 4, and 6 hours postdose on Cycle 1 Day 1 and Cycle 1 Day 22 for all subjects in Part 1.

Acalabrutinib PK blood sampling (2 mL per sample) will be collected. For Part 1, samples will be collected from all subjects on Cycle 1 Day 1 and Cycle 1 Day 22 predose and at approximately 1, 2, 4 and 6 hours postdose.

The predose sample can be taken up to 30 minutes before dosing. The window for other timepoints is ± 5 minutes. Leftover plasma from PK analysis may be repurposed for exploratory acalabrutinib and/or vistusertib plasma metabolite analysis. Testing will be done by a central lab. Refer to the laboratory manual for instructions on collection and shipment of PK samples.

4.1.23 Archival Tumor Sample (Required for Study Entry)

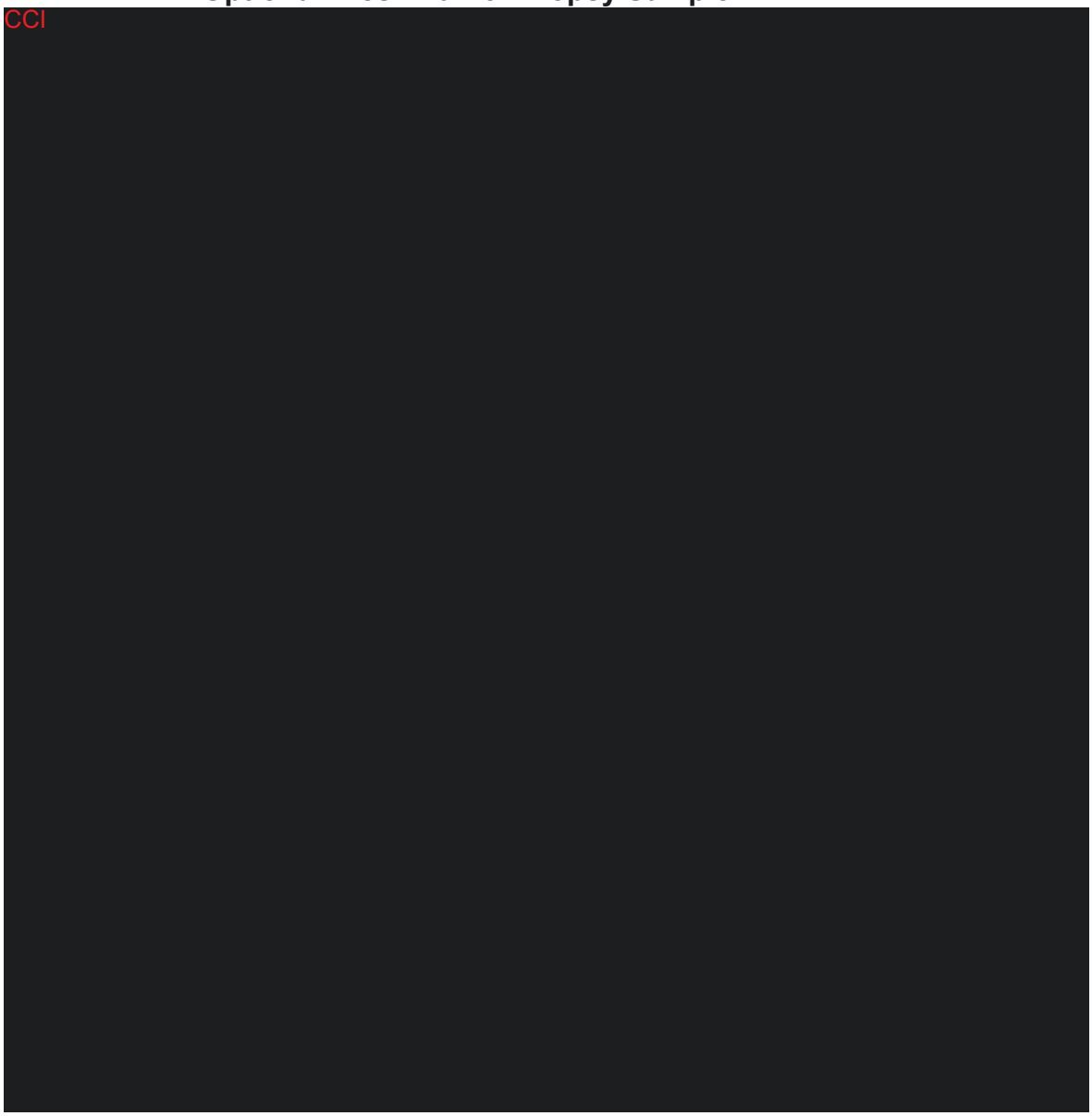
Formalin-fixed tumor tissue embedded in paraffin blocks are to be retrieved for all subjects. If baseline biopsy samples can also be collected, retrieval of the archival diagnostic tumor material is still highly encouraged, to provide data on how the tumor has evolved since diagnosis. The archival samples are preferably from excisional

biopsies from the primary tumor and/or metastatic site. Freshly prepared unstained slides (minimum of 20 is preferred) 4 to 5 micron sections from the archival tumor block are acceptable, if tumor blocks cannot be submitted. Because uncontrolled oxidation processes affect tumor sections, tumor tissue blocks are preferred. From submitted archival tumor blocks, 2 cores may be removed to construct tissue microarrays for later biomarker analysis. The remaining part of the tumor block will be returned to the institution.

Details of sample collection, processing, shipping, and storage will be described in the laboratory manual.

4.1.24 Optional Fresh Tumor Biopsy Sample

CCI



4.1.25 Pharmacodynamic Samples

CCI

[redacted]

4.1.26 ctDNA Samples

CCI

[redacted]

4.1.27 Exploratory Blood Biomarker Samples

CCI

[redacted]

4.1.28 Optional Pharmacogenetics Sample

CCI

[redacted]

4.1.29 Bone Marrow Biopsy/Aspirate

Bone marrow biopsy and aspirate with flow cytometry analysis at baseline will be performed locally to show any bone marrow involvement for all subjects.

A further bone marrow biopsy and aspirate is required to confirm a CR, if the baseline sample is positive.

4.1.30 Tumor Assessments

For all histologies:

Baseline tumor assessments will be performed using radiologic imaging by CT with contrast and PET-CT covering neck, chest, abdomen, and pelvis within 30 days before the first dose of study drug. Radiologic scans (ie, contrast CT) will be repeated every *3* cycles (ie, approximately every *12* weeks ± 7 days). PET-CT also will be repeated on the same schedule, when required, per Section 4.3 of the protocol. For subjects with baseline hepatosplenomegaly, the cranial-caudal measurement of the spleen and longest diameter of the liver will be assessed at screening and subsequent response evaluations.

MRI may be used for imaging assessments if a contrast CT scan is contraindicated or unobtainable. In cases where MRI is desirable, the MRI must be obtained at baseline and at all subsequent response evaluations.

4.1.31 Study Drug Accountability

See Section 7.6.

4.2 BIOLOGIC SAMPLING PROCEDURES

4.2.1 Handling, Storage, and Destruction of Biologic Samples

Refer to the laboratory manual for specific guidelines and instructions.

The samples will be used up, or disposed of, after analyses or retained for further use as described here.

Biologic samples for future research will be retained at the Research & Development site, on behalf of AstraZeneca for a maximum of 15 years after the last subject's last visit in the study. The results from future analysis will not be reported in the CSR, but separately in a Scientific Report.

4.2.2 Pharmacokinetic Samples

PK samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses, such as metabolite testing.

PK samples may be disposed of, or destroyed, and anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR. Anonymized samples will be retained for ≤5 years after the CSR is finalized.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but separately in a Bioanalytical Report.

4.2.3 Samples for Exploratory Research

CCI

CCI

[redacted]

4.2.4 Chain of Custody of Biologic Samples

CCI

[redacted]

4.2.5 Withdrawal of Informed Consent for Donated Biological Samples

Subjects may withdraw from any aspects of the voluntary exploratory research at any time, without prejudice to further treatment and independent of any decision concerning participation in other aspects of the main study.

If a subject withdraws consent for use of donated biologic samples, then the samples will be disposed of/destroyed, and the action documented. If samples are already analyzed, the sponsor is not obliged to destroy the results of this research.

If consent to use of biologic samples is withdrawn, the subject may continue in the study.

The investigator:

- Ensures the sponsor is notified immediately of the subject's withdrawal of informed consent to the use of donated biologic samples
- Ensures that biologic samples from that subject, if stored at the study site, are immediately identified, disposed of/destroyed, and the action documented
- Ensures the local laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site
- Ensures that the subject and the sponsor are informed about the sample disposal.

The sponsor and AstraZeneca ensure the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the document returned to the study site.

4.3 INVESTIGATOR'S ASSESSMENT OF RESPONSE TO TREATMENT

Tumor assessments will be made for measurable disease, non-measurable disease, and new lesions on CT and combined with visual assessment of PET-CT for response assessment according to the revised response criteria for malignant lymphoma (Cheson et al 2014 in Appendix 9).

CT scans

Bidimensional measurements will be recorded for lymph nodes ≥1.5 cm in longest diameter in the eCRF.

Up to a maximum of 6 dominant, measurable lymph nodal lesions should be assessed as target lesions. These nodes or masses should be selected according to all of the following:

- They should be clearly measurable in at least 2 perpendicular dimensions

- If possible they should be from disparate regions of the body
- They should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

The perpendicular long and short axis diameters will be measured and recorded in the transverse plain at baseline and follow-up. When appropriate, measurable extranodal disease (eg, hepatic nodules) may be included in the 6 representative, measured lesions.

For the selected target lymph nodal lesions, the sum of the product of the perpendicular diameters will be calculated with the percentage change from baseline for assessment of response and nadir for assessment of progression.

All other lesions (including nodal, extranodal, and assessable disease) should be followed as nonmeasured disease (eg, cutaneous, GI, bone, spleen, liver, kidneys, pleural or pericardial effusions, ascites) and should be factored into overall response assessment.

Table 11. Revised criteria for response assessment for non-Hodgkin lymphoma (NHL)

Response and Site	PET-CT Based response	CT-Based Response
Complete:	Complete metabolic response:	Complete radiologic response (all of the following):
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS† It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to ≤1.5 cm in LDi No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative

Table 11. Revised criteria for response assessment for non-Hodgkin lymphoma (NHL)

Response and Site	PET-CT Based response	CT-Based Response
Partial: Lymph nodes and extralymphatic sites	Partial metabolic response: Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	Partial remission (all of the following): ≥50% decrease in SPD of up to 6 target measureable nodes and extranodal sites
	At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	When a lesion is too small to measure on CT, assign 5 mm x 5 mm as the default valve When no longer visible 0 x 0 mm For a node >5 mm x 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by >50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease: Target nodes/nodal masses, extranodal lesions	No metabolic response: Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	Stable disease: <50% decrease from baseline in SPD of up to 6 dominant, measureable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change form baseline	Not applicable
Progressive disease: Individual target nodes/nodal masses	Progressive metabolic disease: Score 4 or 5 with an increase in intensity of uptake from baseline and/or	Progressive disease requires at least 1 of the following PPD progression: An individual node/lesion must be abnormal with: LDi >1.5 cm and Increase by ≥ 50% from PPD nadir and

Table 11. Revised criteria for response assessment for non-Hodgkin lymphoma (NHL)

Response and Site	PET-CT Based response	CT-Based Response
		An increase in LDi or SDi from nadir 0.5 cm for lesions ≤2 cm 1.0 cm for lesions >2 cm
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of pre-existing nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node >1.5 cm in any axis A new extranodal site >1.0 cm in any axis; if <1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS, 5-point scale; CT computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trails involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid under treatment). Measured dominant lesions: Up to 6 of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in 2 diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver spleen, kidneys, and lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy of myeloid growth factors).

†PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

Visual interpretation of PET-CT scans

The International Working Group criteria for reviewing PET scans were based on visual interpretation, using mediastinal blood pool as the comparator. The current recommendation is to use the 5-point scale (Cheson et al 2014).

Assessment of non-measurable lesions

An overall assessment will be made for all other non-target lesions of present, absent or present with progression will be recorded and factored into response assessment.

Assessment of new lesions

Appearance of any new lesions more than 1.5 cm in any axis during or at the end of therapy, even if all other lesions are decreasing should be considered progression.

Increased FDG uptake in a previously unaffected site should only be considered progression after confirmation with other modalities (eg, CT, MRI or x-ray).

In subjects with no history of pulmonary lymphoma, new nodules identified by CT are benign and should be considered negative for lymphoma. These lesions typically represent infectious or inflammatory lesions and therefore if FDG positive should not be considered positive for lymphoma in the absence of confirmatory tests, eg, histology.

The presence or absence of new lesions will be recorded on the eCRF.

4.4 SAFETY FOLLOW-UP (SFU) VISITS

Each subject should be followed until the SFU visit at 30 (+7) days after his or her last dose of study drug to monitor for resolution or progression of AEs and to document the occurrence of any new events, regardless of whether the subject receives a new anticancer therapy or demonstrates disease progression within this timeframe. Subjects who withdraw consent for study treatment should still be encouraged to complete the SFU assessments before withdrawing consent, but these assessments cannot be mandated if subject consent for further study participation is withdrawn. The Schedule of Assessments (Appendix 1and Appendix 2) describes the procedures required for the SFU visit.

4.5 FOLLOW-UP FOR PROGRESSION AND SURVIVAL

Subjects who discontinue both study drugs before documented disease progression will be followed according to standard of care until documented disease progression is captured in the EDC system. During this period, information will also be collected in the

EDC system on any new anticancer agents and on any SAEs considered related to study drug(s) or study procedures. The long-term follow up will not apply to subjects who withdraw consent or are lost to follow-up.

All subjects will be followed for survival until death, loss to follow up, sponsor decision to stop trial, or withdrawal of consent, whichever occurs first. Subjects will be followed for survival by telephone calls or clinic visits approximately every 3 months. During this period, information will also be collected on any SAEs considered related to study drug(s) or study procedures.

4.6 MISSED EVALUATIONS

Missed evaluations should be rescheduled and performed as close to the original scheduled date as possible. An exception is made when rescheduling becomes, in the investigator's opinion, medically unnecessary or unsafe because it is too close in time to the next scheduled evaluation. In that case, the missed evaluation should be abandoned.

5.0 STATISTICAL METHODS OF ANALYSIS

5.1 GENERAL CONSIDERATIONS

Descriptive statistics (including means, standard deviations, and medians for continuous variables and proportions and confidence intervals [CIs] for discrete variables) will be used to summarize data as appropriate. Response rate will be investigator assessed using standard response criteria (Cheson et al 2014). KM methods will be used to estimate DOR, PFS, OS and corresponding quartiles (including the median).

5.2 RATIONALE FOR SAMPLE SIZE

In Part 1 (dose selection), enrollment of 6 subjects per dose level limits the number of subjects exposed consistent with the expected safety profiles of the study drugs, but includes sufficient subjects to explore effects on PD biomarkers of BTK and mTOR inhibition. The trial employ*ed* the standard NCI definition of MTD (dose associated with DLT in <33.3% of subjects assessed during cycle 1).

A maximum of 3 dose levels *were to have been* explored in each of the two schedules (continuous/intermittent vistusertib dosing). The maximum number of subjects in Part 1 *was* therefore 36. *The sponsor stopped the study in Part 1 after treating 25 subjects with the first 2 dose levels of vistusertib.*

5.3 DEFINITION OF ANALYSIS SETS

The analysis of data will be based on different subsets according to the purpose of the analysis.

Analysis sets are presented in Table 12.

Table 12. Analysis sets

Analysis set	Definition
Safety	All subjects who took ≥1 dose of either study drug. Data will be presented by initial dose received.
Pharmacokinetics	All subjects in the safety analysis set with evaluable PK parameters.
Efficacy	All subjects in the safety analysis set with a baseline tumor assessment. Data will be presented by planned dose.

5.4 MISSING DATA HANDLING

No imputation of values for missing data will be performed except that missing or partial start and end dates for AEs and concomitant medication will be imputed according to prespecified, conservative imputation rules. Subjects lost to follow-up (or drop out) will be included in statistical analyses to the point of their last evaluation.

5.5 OUTCOME DATA ANALYSIS

5.5.1 Safety

Verbatim descriptions of AEs will be mapped according to the MedDRA thesaurus terms and graded according to NCI CTCAE, v*5.0* or higher. Extent of exposure to study drug(s), all AEs, SAEs, any adverse events leading to study drug(s) discontinuation, and study drug(s) related-adverse events will be summarized. The frequency of AEs will be summarized by system organ class and preferred terms according to MedDRA, as well as per severity per NCI CTCAE grade. Treatment-emergent AEs will be summarized, unless otherwise specified. For events with varying severity, the worst reported grade will be used.

Laboratory abnormalities will be defined based on laboratory normal ranges (universal normal ranges, if central lab). Selected laboratory parameters may be analyzed with shift tables and summaries of changes from baseline to worst post-treatment value.

Vital sign assessments will be tabulated and summarized.

5.5.2 Demographics and Baseline Characteristics

Analyses will include summaries of subject demographics, baseline characteristics, and concurrent treatments. Concomitant medications will be coded and tabulated according to the World Health Organization Drug Dictionary (WHODRUG).

5.5.3 Exposure to Study Drug(s)

Descriptive statistics (n, mean, standard deviation, median, and range) will be used to summarize the following:

- duration of exposure (the interval between first dose date and last dose date)
- average daily dose (the ratio of total dose administered and treatment duration)
- relative dose intensities (the ratio of total actual dose and total planned dose)

5.5.4 Analysis of Efficacy Parameters

5.5.4.1 Overall Response Rate (ORR) and Complete Response (CR) Rate

The ORR is defined as the rate of subjects who achieve either a PR or CR, according to the revised response criteria for malignant lymphoma (Cheson et al 2014), as assessed by investigators before receiving any other anticancer therapy. ORR and CR will be presented by histology. The corresponding 95% two-sided CI will be derived for ORR and CR rate.

5.5.4.2 Progression-Free Survival (PFS)

Disease progression will be determined by the investigators according to the revised response criteria for malignant lymphoma (Cheson et al 2014). PFS is defined as the time from first dose date to documented disease progression, or death from any cause, whichever occurs first. Subjects who had the event after the start of subsequent therapy, or who are progression-free and alive at the time of data cutoff, or have unknown status will be censored at the time of their last disease assessment on or before the start of subsequent therapy or data cut-off. Subjects with no post-baseline disease assessment will be censored on Day 1. KM curves may be presented by histology, if appropriate. KM estimates and corresponding two-sided 95% CIs will be calculated for the median and quartiles.

5.5.4.3 Duration of Response (DOR)

DOR is defined as the time from the first objective response of CR or PR to the time of documented disease progression or death due to any cause, whichever occurs first. Subjects who had the event after the start of subsequent therapy, or are progression-

free and alive at the time of data cutoff, or have unknown status will be censored at the last tumor assessment on or before the start of subsequent therapy. Plots will be used to show the durations of responses. KM curves may be presented by histology, if appropriate. KM estimates and corresponding two-sided 95% CIs will be calculated for the median and quartiles.

5.5.4.4 Durable Response Rate (DRR)

The DRR is defined as the percentage of subjects who have a complete or partial response lasting ≥8 weeks.

5.5.4.5 Overall Survival (OS)

OS is defined as the time from first dose until the date of death from any cause. Subjects who have not died by the analysis data cutoff date will be censored at their last date known to be alive before the cutoff date. Subjects known to be alive or dead after the data cutoff date will be censored at the data cutoff date. Subjects who are lost in follow-up will be censored at the date the subject is last known to have been alive. KM curves may be presented by histology, if appropriate. KM estimates and corresponding two-sided 95% CIs will be calculated for the median and quartiles.

5.5.5 Pharmacokinetic Analyses

The plasma PK of acalabrutinib and vistusertib will be characterized using noncompartmental analysis. The following PK parameters will be calculated, whenever possible, from plasma concentrations of analytes *(Note: These will not be collected or assessed for subjects whose study participation extends past the first 12 cycles.)*:

- $AUC_{0\text{-last}}$: Area under the plasma concentration-time curve calculated using linear trapezoidal summation from time 0 to time last, where “last” is the time of the last measurable concentration
- $AUC_{0\text{-inf}}$: Area under the plasma concentration-time curve from 0 to infinity, calculated using the formula: $AUC_{0\text{-inf}} = AUC_{0\text{-last}} + C_{last} / \lambda_z$, where λ_z is the apparent terminal elimination rate constant
- C_{max}: Maximum observed plasma concentration
- T_{max}: Time of the maximum plasma concentration (obtained without interpolation)
- $t_{½}$: Terminal elimination half-life (whenever possible)
- λ_z: Terminal elimination rate constant (whenever possible)
- CL/F: Oral clearance
- V_z/F: Oral volume of distribution

5.5.6 Additional PK and PD Analyses

Additional PD and PK analyses may be performed, as deemed appropriate.

6.0 ASSESSMENT OF SAFETY

Safety assessments will consist of monitoring and recording DLTs, AEs, SAEs and AEs leading to discontinuation of study drug(s); measurements of protocol-specified hematology, clinical chemistry, and other laboratory variables; measurement of protocol-specified vital signs and ECGs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug(s).

6.1 DEFINITIONS

6.1.1 Adverse Events

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational (medicinal) product, regardless of attribution.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol specified AE reporting period, including signs or symptoms associated with lymphoma that were not present before the AE reporting period (see Section 6.2.1).
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.
- Abnormal laboratory values considered clinically significant by the investigator should be reported as an AE.

The following are NOT considered an AE:

- Pre-existing condition that has not worsened: A pre-existing condition (documented on the medical history eCRF) is not considered an AE unless the severity, frequency, or character of the event worsens during the study period.
- Preplanned hospitalization: A hospitalization planned before signing the ICF is not considered an SAE, but rather a therapeutic intervention. However, if during the preplanned hospitalization an event occurs, which prolongs the

hospitalization or meets any other SAE criteria, the event will be considered an SAE. Surgeries or interventions that were under consideration, but not performed before signing the ICF, will not be considered serious if they are performed after signing the ICF for a condition that has not changed from its baseline level. Elective hospitalizations for social reasons, solely for the administration of chemotherapy, or due to long travel distances are also not SAEs.

- Diagnostic testing and procedures: Testing and procedures should not be reported as AEs or SAEs, but rather the cause for the test or procedure should be reported. If a test or procedure is done to rule out a diagnosis, the sign or symptom leading to the test/procedure should be the event term, and the event term should only be updated to the diagnosis if/when the diagnosis is confirmed. Testing and procedures performed solely as screening measures (eg, routine screening mammography or colonoscopy) should not be reported as AEs or SAEs.
- Abnormal laboratory results that the investigator considers to not be clinically significant: Abnormal laboratory results are not AEs unless they are clinically significant. For example, a clinically significant laboratory results is one that requires treatment (for example a blood transfusion for low hemoglobin) or requires a change in study drug (eg, lowering the dose or withholding study drug while the laboratory finding resolves or stabilizes).
- Progression of underlying malignancy: Progression of underlying malignancy will not be reported as an AE if it is clearly consistent with the suspected progression of the underlying cancer. Hospitalization due solely to the progression of underlying malignancy should NOT be reported as an SAE. Clinical symptoms of progression may be reported as AEs if the symptoms cannot be determined as exclusively due to the progression of the underlying malignancy, or if they do not fit the expected pattern of progression for the disease under study.

  If there is any uncertainty about an AE being due only to the disease under study, it should be reported as an AE or SAE.

6.1.2 Serious Adverse Event

The terms “severe” and “serious” are not synonymous. Severity (or intensity) refers to the grade of an AE (see below). “Serious” is a regulatory definition and is based on

subject or event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations from the sponsor to applicable regulatory authorities.

An AE should be classified as an SAE if it meets any 1 of the following criteria:

- It results in death (ie, the AE actually causes or leads to death).
- It is life-threatening (ie, the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (ie, the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product.
- It is considered a significant medical event by the investigator based on medical judgment (eg, may jeopardize the subject or may require medical/surgical intervention to prevent 1 of the outcomes listed above).

6.1.3 Severity

Definitions found in the CTCAE version *5.0* or higher will be used for grading the severity (intensity) of AEs. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a subject experience any AE not listed in the CTCAE, the following grading system should be used to assess severity:

- Grade 1 (Mild AE) – experiences which are usually transient, requiring no special treatment, and not interfering with the subject's daily activities
- Grade 2 (Moderate AE) – experiences which introduce some level of inconvenience or concern to the subject, and which may interfere with daily activities, but are usually ameliorated by simple therapeutic measures
- Grade 3 (Severe AE) – experiences which are unacceptable or intolerable, significantly interrupt the subject's usual daily activity, and require systemic drug therapy or other treatment
- Grade 4 (Life-threatening or disabling AE) – experiences which cause the subject to be in imminent danger of death
- Grade 5 (Death related to AE) – experiences which result in subject death

6.2 DOCUMENTING AND REPORTING OF ADVERSE AND SERIOUS ADVERSE EVENTS

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, as outlined in the prior sections, are recorded on the eCRF. All SAEs must be reported on the SAE form or clinical database.

6.2.1 Adverse Event Reporting Period

After the signing of the ICF, all SAEs must be reported. After the first dose of study drug(s), all AEs/SAEs, irrespective of attribution of causality, must be reported.

AE reporting, irrespective of seriousness, ends 30 days after the last dose of study drug(s).

SAEs considered related to study drug(s) or study procedures occurring after the end of the AE reporting period (as defined above) must be reported.

If an SAE is present at the last study visit, the SAE should be followed to resolution or until the investigator assesses the subject as stable, or the subject is lost to follow-up or withdraws consent. Resolution/stable means the subject has returned to baseline state of health or the investigator does not expect any further improvement or worsening of the event.

6.2.2 Assessment of Adverse Events

Investigators will assess the occurrence of AEs and SAEs at all subject evaluation timepoints during the study. All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, or other means, will be recorded in the subject's medical record and on the AE eCRF.

Disease progression itself is not considered an AE.

Each recorded AE or SAE will be described by its diagnostic term, duration (eg, start and end dates), severity, regulatory seriousness criteria, if applicable, suspected relationship to the study drug (see following guidance), and any actions taken. The causality of AEs to the study drug will be assessed by means of the question: 'Is there a reasonable possibility that the event may have been caused by the study drug?' per FDA guidance on safety reporting requirements (Food and Drug Administration Guidance 2012).

See Appendix 8 for more detail on assessing causality.

6.2.3 Pregnancy

The investigator should report pregnancies in female subjects or in the partners of male subjects within 24 hours using the Pregnancy Report Form. This form should be faxed or emailed to Acerta Pharma Drug Safety. Any pregnancy-associated SAE must be reported to Acerta Pharma, according to the usual timelines and directions for SAE reporting (see Section 6.2.4).

Any uncomplicated pregnancy that occurs during this study will be reported. All pregnancies that are identified during or after this study, wherein the estimated date of conception is determined to have occurred from the time of consent to *2* days after the last dose of *acalabrutinib or 16 weeks after the last dose of vistusertib, whichever is longe*r, will be reported, followed to conclusion, and the outcome reported, as long as the subject or subject's partner is willing to participate in follow up. Upon completion of the pregnancy, additional information on the mother, pregnancy, and baby will be collected and sent to CCI .

A pregnancy itself is not regarded as an AE unless there is suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Likewise, elective abortions without complications are not considered AEs. Any SAEs associated with pregnancy (eg, congenital abnormalities/birth defects/spontaneous miscarriage or any other serious events) must additionally be reported as such using the SAE report form.

Subjects should be instructed to immediately notify the investigator of any pregnancies.

6.2.4 Expedited Reporting Requirements for Serious Adverse Events

All SAEs must be reported within 24 hours of discovery. All initial SAE reports and follow-up information will be reported using the protocol-specific electronic data capture system. If electronic SAE reporting is not available, paper SAE forms must be emailed or faxed to Acerta Pharma Drug Safety, or designee. Acerta Pharma may request follow-up and other additional information from the investigator (eg, hospital admission/discharge notes and laboratory results).

Whenever possible, AEs/SAEs should be reported by diagnosis term not as a constellation of symptoms.

Death due to disease progression should be recorded on the appropriate form in the EDC system. If the primary cause of death is disease progression, the death due to

disease progression should not be reported as an SAE. If the primary cause of death is something other than disease progression, then the death should be reported as an SAE with the primary cause of death as the event term, as death is typically the outcome of the event, not the event itself. The primary cause of death on the autopsy report should be the term reported. Autopsy and postmortem reports must be forwarded to Acerta Pharma Drug Safety, or designee, as outlined above.

If study drug is discontinued because of an SAE, this information must be included in the SAE report.

An SAE may qualify for mandatory expedited reporting to regulatory authorities if the SAE is attributable to the investigational product (or if a causality assessment is not provided for the SAE, in which case a default of 'related' may be used for expedited reporting purposes) and the SAE is not listed in the current Investigator Brochure (ie, an unexpected event). In this case, Acerta Pharma Drug Safety/Designee will forward a formal notification describing the suspected unexpected serious adverse reaction (SUSAR) to all investigators. Each investigator must then notify his or her IRB/IEC of the SUSAR.

Drug Safety Contact Information	
Fax:	PPD (United States)
	PPD (for outside United States)
Email:	PPD

6.2.5 Type and Duration of Follow-up of Subjects after Adverse Events

All AEs and SAEs that are encountered during the protocol-specified AE reporting period should be followed to resolution, or until the investigator assesses the subject as stable, or the subject is lost to follow-up or withdraws consent.

7.0 STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS

Acerta Pharma retains the right to terminate the study and remove all study materials from a study site at any time. Specific circumstances that may precipitate such termination are:

- Unsatisfactory subject enrollment with regard to quality or quantity
- Significant or numerous deviations from study protocol requirements, such as failures to perform required evaluations on subjects and maintain adequate study records
- Inaccurate, incomplete and/or late data recording on a recurrent basis
- The incidence and/or severity of AEs in this or other studies indicating a potential health hazard caused by the study treatment

7.1 INSTITUTIONAL REVIEW BOARD AND INDEPENDENT ETHICS COMMITTEE

The investigator will submit this protocol, the informed consent, Investigator Brochure, and any other relevant supporting information (eg, all advertising materials) to the appropriate IRB/IEC for review and approval before study initiation. A signed protocol approval page; a letter confirming IRB/IEC approval of the protocol and informed consent; and a statement that the IRB/IEC is organized and operates according to Good Clinical Practice (GCP) guidelines and the applicable laws and regulations; **must** be forwarded to Acerta Pharma **before** screening subjects for the study. Additionally, sites must forward a signed Form FDA 1572 (Statement of Investigator) to Acerta Pharma before screening subjects for study enrollment. Amendments to the protocol must also be approved by the IRB/IEC and local regulatory agency, as appropriate, before the implementation of changes in this study.

7.2 INFORMED CONSENT AND PROTECTED SUBJECT HEALTH INFORMATION AUTHORIZATION

A copy of the IRB/IEC-approved informed consent must be forwarded to Acerta Pharma for regulatory purposes. The investigator, or designee (designee must be listed on the Study Personnel Responsibility/Signature Log, see Section 7.11), **must** explain to each subject the purpose and nature of the study, the study procedures, the possible adverse effects, and all other elements of consent as defined in § 21 Code of Federal Regulations (CFR) Part 50, and other applicable national and local regulations governing informed consent form. Each subject must provide a signed and dated informed consent before enrollment into this study. If allowed by the protocol, a legal representative may sign the informed consent form for a subject incapable of giving consent. Signed consent forms must remain in each subject's study file and be available for verification by study monitors at any time.

In accordance to individual local and national patient privacy regulations, the investigator or designee **must** explain to each subject that for the evaluation of study results, the subject's protected health information obtained during the study may be shared with Acerta Pharma and its designees, regulatory agencies, and IRBs/IECs. As the study sponsor, Acerta Pharma will not use the subject's protected health information or disclose it to a third party without applicable subject authorization. It is the investigator's or designee's responsibility to obtain written permission to use protected health information from each subject, or if appropriate, the subject's legal guardian. If a subject or subject's legal guardian withdraws permission to use protected health information, it is the investigator's responsibility to obtain the withdrawal request in writing from the subject or subject's legal guardian **and** to ensure that no further data will be collected from the subject. Any data collected on the subject before withdrawal will be used in the analysis of study results.

7.3 SUBJECT SCREENING LOG

The investigator must keep a record that lists **all** subjects considered for enrollment (including those who did not undergo screening) in the study. For those subjects subsequently excluded from enrollment, record the reason(s) for exclusion.

7.4 CASE REPORT FORMS

Authorized study site personnel (see Section 7.11) will complete eCRFs designed for this study according to the completion guidelines that will be provided within the clinical database. The investigator will ensure that the eCRFs are accurate, complete, legible, and completed promptly. Refer to Section 7.7 for record retention requirements.

7.5 STUDY MONITORING REQUIREMENTS

Representatives of Acerta Pharma or its designee will monitor this study until completion. The purpose of monitoring is to ensure compliance with the protocol and the quality and integrity of the data. This study is also subject to reviews or audits.

Every effort will be made to maintain the anonymity and confidentiality of all subjects during this clinical study. However, because of the experimental nature of this treatment, the investigator agrees to allow the IRB/IEC, representatives of Acerta Pharma, its designated agents, and authorized employees of the appropriate regulatory agencies to inspect the facilities used in this study and, for purposes of verification, allow direct access to the hospital or clinic records of all subjects enrolled into this study. This

includes providing by fax, email, or regular mail de-identified copies of radiology, pathology, and/or laboratory results when requested by the sponsor. A statement to this effect will be included in the informed consent and permission form authorizing the use of protected health information.

7.6 INVESTIGATIONAL STUDY DRUG ACCOUNTABILITY

Study drug must be kept in a locked limited access cabinet or space. The study drug must not be used outside the context of the protocol.

Study drug accountability records must be maintained and readily available for inspection by representatives of Acerta Pharma and are open to inspections by regulatory authorities at any time.

All study supplies and associated documentation will be regularly reviewed and verified by the monitor.

7.7 RECORD RETENTION

The investigator and other appropriate study staff are responsible for maintaining all documentation relevant to the study. Mandatory documentation includes copies of study protocols and amendments, each Form FDA 1572, IRB/IEC approval letters, signed ICFs, drug accountability records, SAE information transmitted to Acerta Pharma, subject files (source documentation) that substantiate entries in eCRFs, all relevant correspondence and other documents pertaining to the conduct of the study.

An investigator shall retain records for a period of at least 2 years after the date the last marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. The investigator must notify Acerta Pharma and obtain written approval from Acerta Pharma before destroying any clinical study records at any time. Acerta Pharma will inform the investigator of the date that study records may be destroyed or returned to Acerta Pharma.

Acerta Pharma must be notified in advance of, and Acerta Pharma must provide express written approval of, any change in the maintenance of the foregoing documents if the investigator wishes to move study records to another location or assign responsibility for record retention to another party. If the investigator cannot guarantee the archiving requirements set forth herein at his or her study site for all such documents, special

arrangements must be made between the investigator and Acerta Pharma to store such documents in sealed containers away from the study site so that they can be returned sealed to the investigator for audit purposes.

7.8 PROTOCOL AMENDMENTS

Acerta Pharma will initiate any change to the protocol in a protocol amendment document. The amendment will be submitted to the IRB/IEC together with, if applicable, a revised model ICF. If the change in any way increases the risk to the subject or changes the scope of the study, then written documentation of IRB/IEC approval must be received by Acerta Pharma before the amendment may take effect. Additionally under this circumstance, information on the increased risk and/or change in scope must be provided to subjects already actively participating in the study, and they must read, understand, and sign any revised ICF confirming willingness to remain in the trial.

7.9 PUBLICATION OF STUDY RESULTS

Authorship, in general, will follow the recommendations of the International Committee of Medical Journal Editors (2015).

7.10 CLINICAL TRIAL INSURANCE

Clinical trial insurance has been undertaken according to the laws of the countries where the study will be conducted. An insurance certificate will be made available to the participating sites at the time of study initiation.

7.11 GENERAL INVESTIGATOR RESPONSIBILITIES

The principal investigator must ensure that:

1. He or she will personally conduct or supervise the study.
2. His or her staff and all persons who assist in the conduct of the study clearly understand their responsibilities and have their names included in the Study Personnel Responsibility/Signature Log.
3. The study is conducted according to the protocol and all applicable regulations.
4. The protection of each subject's rights and welfare is maintained.
5. Signed and dated informed consent and, when applicable, permission to use protected health information are obtained from each subject before conducting nonstandard of care study procedures. If a subject or subject's legal guardian withdraws permission to use protected health information, the investigator will obtain a written request from the subject or subject's legal guardian and will ensure that no further data be collected from the subject.

6. The consent process is conducted in compliance with all applicable regulations and privacy acts.
7. The IRB/IEC complies with applicable regulations and conducts initial and ongoing reviews and approvals of the study.
8. Any amendment to the protocol is submitted promptly to the IRB/IEC.
9. Any significant protocol deviations are reported to Acerta Pharma and the IRB/IEC according to the guidelines at each study site.
10. eCRF pages are completed promptly.
11. All IND Safety Reports/SUSAR Reports are submitted promptly to the IRB/IEC.
12. All SAEs are reported to Acerta Pharma Drug Safety/Designee within 24 hours of knowledge via the clinical database and to the IRB/IEC per their requirements.

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9.0 APPENDICES

Appendix 1. Schedule of Assessments (Acalabrutinib + Vistusertib)

Assessment	Screen[a]	Cycle 1 (28 Days)				Cycles 2-6 (28 Days)		Cycles 7–12 [cc] (28 Days)	*Extended Study Treatment [cc], >12 cycles (every 12 weeks)*	Assess Disease Every *12* weeks (~*3* Cycles)	30-Day SFU[dd]
		Days				Days		Day	*Day*		
		1	8	15	22	1	15	1	*1*		
		(±2 Day)				(±2 Days)		(±7 Days)	*(±7 Days)*	(±7 Days)	(+7 days)
Informed consent[b]	X										
Inclusion/exclusion	X										
Medical history and demographics	X										
Physical examination[c]	X	X	X	X	X	X	X	X			X
ECOG performance status	X	X				X		X			X
Vital signs[d] and weight	X	X	X	X	X	X	X	X			X
Cumulative Illness Rating Scale (Geriatric)	X										
12-lead ECG[e]	X	X	X	X	X	X					X
Cardiac troponin	X	X		X		X					X
ECHO/MUGA[f]	X										X
Hematology[g]	X	X	X	X	X	X	X	X			X
Serum chemistry[h]	X	X	X	X	X	X	X	X			X
Pregnancy test (women of childbearing potential)	X	X				X		X			X
Urinalysis[i]	X	X				X		X			X
Coagulation (PT/INR/PTT)	X										

Assessment	Screen[a]	Cycle 1 (28 Days)				Cycles 2-6 (28 Days)		Cycles 7–12 [cc] (28 Days)	*Extended Study Treatment [cc], >12 cycles (every 12 weeks)*	Assess Disease Every *12* weeks (~*3* Cycles)	30-Day SFU[dd]
		Days				Days		Day	*Day*		
		1	8	15	22	1	15	1	*1*		
		(±2 Day)				(±2 Days)		(±7 Days)	*(±7 Days)*	(±7 Days)	(+7 days)
Hepatitis serology [j]	X										
HBV PCR [k]	X					X		QM			X
HCV PCR [l]	X					C6					
CMV testing [m]	X					C6		C12			
T/B/NK cell count		X				C2; C3; C6		C9; C12			X
Serum Ig		X				C2; C3; C6		C9,C12			X
Archival tumor sample [n]	X										
Concomitant medication/procedures	X	X	X	X	X	X	X	X	*X*		X
Adverse event evaluation [o]		X	X	X	X	X	X	X	*X*		X
Vistusertib PK [p]		X			X						
Acalabrutinib PK Part 1[q]		X			X						
CCI [redacted]		[redacted]			[redacted]					[redacted]	
CCI [redacted]	[redacted]	[redacted]	[redacted]							[redacted]	

Assessment	Screen[a]	Cycle 1 (28 Days)				Cycles 2-6 (28 Days)		Cycles 7–12 [cc] (28 Days)	*Extended Study Treatment [cc], >12 cycles (every 12 weeks)*	Assess Disease Every *12* weeks (~*3* Cycles)	30-Day SFU[dd]
		Days				Days		Day	*Day*		
		1	8	15	22	1	15	1	*1*		
		(±2 Day)				(±2 Days)		(±7 Days)	*(±7 Days)*	(±7 Days)	(+7 days)
CCI											
CCI											
CCI											
CT scan of thorax [x]	X										
Tumor assessments CT/MRI/PET scans [y]	X									X	X[dd]
Bone marrow biopsy & aspirate [z]	X									To confirm CR	
Vistusertib (oral) [aa]		twice daily continuous or 2 days on/5 days off				→		→	→		
Acalabrutinib (oral) [bb]		twice daily continuous				→		→	→		
Study drug compliance		X				X		X	*X*		

Abbreviations: C = cycle; CMV = cytomegalovirus; CR = complete remission; CT = computed tomography; ctDNA = circulating tumor DNA; D = day; ECG = electrocardiogram, ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; HBV = hepatitis B virus; HCV = hepatitis C virus; Ig = immunoglobulin; INR = international normalization ratio; LTF = long-term follow-up; MCL = mantle cell lymphoma; magnetic resonance imaging; MUGA = multigated acquisition; NK = natural killer; PCR = polymerase chain reaction; PET = positron-emission tomography; PK = pharmacokinetics; PT = prothrombin time; PTT = partial thromboplastin time; Q3M = every 3 months; QM = every month; SFU = safety follow-up; SOC = standard of care.

a. Screening tests should be performed within 30 days before the first administration of study drug, unless otherwise indicated.

b. Informed consent must be obtained ≤30 days before any protocol-defined screening procedures and before the first dose of study drug(s).
c. The screening physical examination will include, at a minimum, the general appearance of the subject, height (screening only), and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. Symptom-directed physical exams are done thereafter.
d. Vital signs (blood pressure, oxygen saturation, pulse, and temperature) will be assessed after the subject has rested in the sitting position for at least 5 minutes.
e. Subjects should be in supine position and resting for ≥10 minutes before the ECGs. Triplicate ECGs are required at screening and Cycle 6 only, or if clinically indicated, at all other visits, single ECGs are required. If an unscheduled ECG is done at any time, then an electrolyte panel (ie, calcium, magnesium, and potassium) must be done to coincide with the ECG testing.
f. In addition to screening, an ECHO should be done 14 days after an abnormal ECG finding (T wave inversion/flattening), or when clinically indicated. If an ECHO cannot be taken, a multigated acquisition (MUGA) scan to assess left ventricular ejection fraction (LVEF) will be done. In case of any T wave abnormality, the ECHO (or MUGA) should be repeated at the 30-day follow up visit to address the question of recovery, during the off-treatment period.
g. Hematology includes complete blood count (CBC) with differential including, but not limited to white blood cell count, hemoglobin, hematocrit, platelet count, absolute neutrophil count (ANC), and absolute lymphocyte count (ALC).
h. Serum chemistry: albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, blood urea nitrogen (BUN), calcium, chloride, cholesterol, C-peptide, creatinine, glucose, lactate dehydrogenase (LDH), magnesium, phosphate/phosphorus, potassium, sodium, triglycerides, total bilirubin, total protein, and uric acid. If an unscheduled ECG is done at any time, then an electrolyte panel (ie, calcium, magnesium, and potassium) must be done to coincide with the ECG testing.
i. Urinalysis: pH, ketones, specific gravity, bilirubin, protein, blood, and glucose.
j. Hepatitis serology must include hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), hepatitis B core antibody (anti-HBc), and hepatitis C (HCV) antibody. In addition, any subjects testing positive for any hepatitis serology, must have polymerase chain reaction (PCR) testing.
k. Subjects who are anti-HBc positive (or have a known history of HBV infection) should have a quantitative PCR test for HBV DNA performed during screening and monthly thereafter. Monthly monitoring should continue until 12 months after last dose of study drug(s). Any subject with a rising viral load (above lower limit of detection) should discontinue study drug and have antiviral therapy instituted and a consultation with a physician with expertise in managing hepatitis B. As intravenous immunoglobulins (IVIG) may cause false positive hepatitis serology, monthly PCR testing is not required in subjects who are currently receiving or received prophylactic IVIG within 3 months before study enrollment and have a documented negative anti-HBc test before the initiation of IVIG therapy. PCR testing should be performed when clinically indicated (eg, in the setting of rising transaminase levels).
l. Subjects with a known history of hepatitis C or who are hepatitis C antibody positive should have quantitative PCR testing for HCV RNA performed during screening and Cycle 6. No further testing beyond Cycle 6 is necessary if PCR results are negative.
m. CMV testing at screening must include serology testing for CMV immunoglobulin G (IgG), CMV IgM, and CMV PCR testing.
n. Formalin-fixed tumor tissue embedded in paraffin blocks are to be retrieved for all subjects (see Section 4.1.23).
o. A formal assessment of adverse events (AEs) will occur at the visits marked in this table, but AEs reported at any time other time will also be recorded in the electronic case report form (eCRF).
p. Vistusertib pharmacokinetic (PK) blood sampling (2 mL per sample) will be collected at predose and at approximately 1, 2, 4 and 6 hours postdose on Cycle 1 Day 1 and Cycle 1 Day 22 for all subjects in Part 1.
q. Acalabrutinib PK blood sampling (2 mL per sample) will be collected. For Part 1, samples will be collected from all subjects on Cycle 1 Day 1 and Cycle 1 Day 22 predose and at approximately 1, 2, 4 and 6 hours postdose.
r. Acalabrutinib PK blood sampling (2 mL per sample) will be collected.
s. CCI [redacted]
t. Fresh tumor biopsies will be collected from subjects who opt in and have accessible tumors. Biopsies will be collected between screening and at least 3 days before the first dose of study drug (ie, predose sample), 1 hour after dosing on Cycle 1 Day 1, any time on Cycle 1 Day 8 (preferred timepoint) or Cycle 1 Day 22 (if tumor still accessible) and, when possible, at disease progression (which may be at the 30-day SFU visit).
u. CCI [redacted]

v. CCI [redacted]

x. A baseline thorax CT scan must be available for all subjects treated with vistusertib, for retrospective analysis and comparison with a high-resolution CT scan, should it be required, if symptoms of interstitial lung disease occur during study conduct. A separate thorax CT scan is not required if a CT scan is done for baseline tumor assessment as described in footnote y.

y. Baseline tumor assessments will be performed using radiologic imaging by CT with contrast and PET-CT covering neck, chest, abdomen, and pelvis at a minimum within 28 days before the first dose of study drug. Radiologic scans (ie, contrast CT) will be repeated every *3* cycles (ie, approximately every *12* weeks ± 7 days). PET-CT also will be repeated on the same schedule, when required, per Section 4.3 of the protocol. For subjects with baseline hepatosplenomegaly, the cranial-caudal measurement of the spleen and longest diameter of the liver will be assessed at screening and all subsequent response evaluations.

z. Bone marrow biopsy and aspirate with flow cytometry analysis at baseline will be performed locally to show any bone marrow involvement. A further bone marrow biopsy and aspirate is required to confirm a complete response (CR), if the baseline sample is positive.

aa. Refer to the protocol for the dose/schedules of vistusertib evaluated in this protocol.

bb. Acalabrutinib will be taken twice daily beginning with Cycle 1 Day 1. On days of vistusertib dosing, both drugs will be taken simultaneously.

cc. Subjects showing clinical benefit and who are tolerating study treatment may remain on study for up to a total of 12 cycles of treatment. Subjects who have received 12 cycles of treatment (ie, been on study for approximately 12 months) and are deriving clinical benefit from acalabrutinib monotherapy or the combination of acalabrutinib and vistusertib may *remain on study treatment beyond the first 12 months until disease progression occurs or* be eligible to enroll in either a rollover study of acalabrutinib monotherapy or a rollover study of the combination of acalabrutinib and vistusertib, respectively.

dd. The SFU visit will be performed 30 days (+7 days) after the last dose of all study drug(s). Tumor assessments will be repeated at this visit, if they have not been performed within the past 12 weeks.

Appendix 2. Schedule of Assessments (Acalabrutinib Monotherapy)

	Treatment Phase [j]	***Extended Study Treatment >12 cycles*** [j]	**Safety Follow- up Visit**[k]
	Every 3 months (±7 days)	*Every 12 weeks*	30 days (+7 days) after last dose
PE[a]/Vital signs[b]/Weight	X		X
ECOG status	X		X
Lab assessments:			
Hematology[c]	X		X
Serum chemistry[d]	X		X
HBV PCR[e]	QM		
T/B/NK cell count	Every 6 mos		
Serum Ig	Every 6 mos		X
Pregnancy testing (women of childbearing potential)	QM		X
Tumor sample[f]	At disease progression		
CCI [redacted]	[redacted]		
Bone marrow (aspirate/biopsy)[g]	Investigator discretion & to confirm CR		
Pharmacodynamics			X
Acalabrutinib dispensed	X	*X*	
Study drug compliance	X	*X*	
Tumor assessment[h]	X		X
Radiologic assessment[i]	X		X
Concomitant medications	X	*X*	X
Adverse events	X	*X*	X
Disease progression/new anticancer therapy follow-up			
Survival			

Abbreviations: CR = complete remission; CT = computed tomography; DFU = discontinuation follow-up; ECOG = Eastern Cooperative Oncology Group; HBV = hepatitis B virus; Ig = immunoglobulin; LTF = long-term follow-up; mos = months; PE = physical exam; NK = natural killer; PCR = polymerase chain reaction; Q3M = every 3 months; QM = every month; SOC = standard of care

a. Symptom-directed physical exams will be performed.
b. Vital signs (blood pressure, pulse, and body temperature) will be assessed after the subject has rested in the sitting position.
c. Hematology must include complete blood count (CBC) with differential, including, but not limited to white blood cell count, hemoglobin, hematocrit, platelet count, absolute neutrophil count (ANC), and absolute lymphocyte count (ALC).
d. Serum chemistry: albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), magnesium, phosphate/phosphorus, potassium, sodium, total bilirubin, total protein, and uric acid.

e. Subjects who are hepatitis B core antibody (anti-HBc) positive (or have a known history of HBV infection) should have a monthly quantitative polymerase chain reaction (PCR) test for HBV DNA. Monthly monitoring should continue until 12 months after last dose of study drug(s). Any subject with a rising viral load (above lower limit of detection) should discontinue study drug(s) and have antiviral therapy instituted and a consultation with a physician with expertise in managing hepatitis B. As intravenous immunoglobulins (IVIG) may cause false positive serology, monthly PCR testing is not required in subjects who are currently receiving or received prophylactic IVIG within 3 months before study enrollment and have a documented negative anti-HBc before the initiation of IVIG therapy, unless clinically indicated (eg, in the setting of rising transaminase levels).
f. Provide tissue slides from a newly obtained tumor sample at the time of disease progression for exploratory correlative studies.
g. Bone marrow aspirate and biopsy to be done at investigator discretion, per standard of care. Bone marrow and positron-emission tomography/computed tomography (PET/CT) are only required for confirmation of complete remission (CR) per clinical guidelines (see Section 4.3). When possible extra bone marrow tissue may be used for pharmacodynamic evaluation.
h. On-treatment computed tomography (CT) scans will be done every 12 weeks (~3 cycles) or more frequently at the investigator's discretion.
i. PET/CT is only required for confirmation of CR per clinical guidelines (see Section 4.3).
j. Subjects showing clinical benefit and who are tolerating study treatment may remain on study for up to a total of 12 cycles of treatment. Subjects who have received 12 cycles of treatment (ie, been on study for approximately 12 months since first dose of study drug) and are deriving clinical benefit from acalabrutinib monotherapy may *remain on study treatment beyond the first 12 months until disease progression occurs or* be eligible to enroll in a rollover study of acalabrutinib monotherapy.
k. The safety follow-up visit will be performed 30 days (+7 days) after the last dose of all study drug(s). Tumor assessments will be repeated at this visit, if they have not been performed within the past 12 weeks.

Appendix 3. Performance Status Scores

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

As published in Am J Clin Oncol:

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

Credit: Eastern Cooperative Oncology Group Chair: Robert Comis, MD

Available at: http://www.ecog.org/general/perf_stat.html. Accessed 23 August 2013.

Appendix 4. Restricted CYP and Transporter-Related Comedications

Before study start, use of potent or moderate inhibitors or inducers of CYP3A4/5, P-gp and BCRP or substrates of the drug transporters P-gp and BCRP is not permitted within the appropriate washout periods for each drug before the first dose of study treatment until at least after Cycle 1.

Examples of such substances and the corresponding minimum washout periods are presented in Table 13.

Short term administration of such substances during a study may be permitted after the end of Cycle 1 under the following circumstances:

- If a subject requires short-term administration of a restricted CYP3A4/5, P-gp or BCRP inhibitor (see Table 13), vistusertib must be withheld for 3 days before the first dose and not restarted until at least the concomitant therapy has been discontinued for the appropriate washout period.
- If a subject requires short-term administration of a restricted CYP3A4/5, P-gp or BCRP inducer (see Table 13) this should be clearly documented in the eCRF and may be permitted, but this could lead to lower levels of vistusertib and a potential reduction in clinical efficacy.
- If a subject requires short-term administration of restricted substrates of OATP1B1, OATP1B3, MATE1 and MATE2K transporters (see Table 14), vistusertib treatment must be withheld for 3 days prior to the first dose and not restarted until the concomitant therapy has been discontinued for the appropriate washout period (at least 5 times the elimination half-life).

The lists of CYP and transporter inhibitors/inducers and transporter substrates in Table 13 and Table 14 are not exhaustive and the absence of a drug from these lists does not imply that its combination with the study drug(s) is safe.

Table 13. Cytochrome P450 enzyme inhibitors/inducers and transporters restrictions

Category	Examples of drugs	Minimum drug washout period
CYP3A4/5 Potent competitive inhibitors	grapefruit juice, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, saquinovir, telithromycin and troleandomycin and voriconazole	1 week
	idelalisib	2 weeks
CYP3A4/5 Potent Time dependent inhibitors	bocepravir, clarithromycin, cobicistat, danoprevir, elvitegravir, LCL161, lopinavir, mibefradil*, posaconazole, ritonavir, telaprevir and tipranivir	2 weeks
CYP3A4/5 Potent inhibitors (classification unknown)	conivaptan	1 week
CYP3A4/5 Moderate competitive inhibitors	amprenavir, aprepitant, atazanavir, cimetidine, cyclosporine, fluconazole, imatinib and netupitant	1 week
CYP3A4/5 Moderate Time dependent inhibitors	ACT-178882, casopitant, crizotinib, darunavir, diltiazem erythromycin, ledipasvir, lomitapide, tofisopam and verapamil	2 weeks
	FK1706	half-life not found
CYP3A4/5 Moderate inhibitors (classification not known)	ciprofloxacin and dronedarone	1 week
	schisandra sphenanthera	half-life not found
CYP3A4/5 Potent inducers	carbamazepine, phenytoin, rifabutin, rifampicin and St John Wort	3 weeks
	enzalutamide and phenobarbital	5 weeks
	mitotane	114 weeks
	avasimibe	half-life not found
CYP3A4/5 Moderate inducers	bosentan, genistein, lersivirine, lopinavir, modafinil, nafcillin, ritonavir, semagacestat, thioridazine and tipranavir	1 week

Table 13. Cytochrome P450 enzyme inhibitors/inducers and transporters restrictions

Category	Examples of drugs	Minimum drug washout period
	etravirine	2 weeks
	efavirenz	3 weeks
	talviraline	half-life not found
P-gp inhibitors	dronedarone, erythromycin, indinavir, itraconazole, ketoconazole, lapatinib, lopinavir, ritonavir, quinidine and verapamil	1 week
	vorapaxer	10 weeks
	valspodar (PSC 833)	half-life not found
P-gp inducers	carbamazepine and rifampin	3 weeks
BCRP inhibitors	atazanavir, cyclosporine, lopinavir, ritonavir and tipranavir	1 week

Reference: University of Washington database
* discontinued
Strong inhibitor (yielding area under the curve [AUC] ratio ≥5)
Moderate inhibitor (yielding AUC ratio ≥2 and <5)
Strong inducer (AUC decreased by ≥80% or CL increased by more than 5-fold [400%])
Moderate inducer (AUC decreased by 50% to 80% or CL increased by more than 2- to 5-fold [100% to 400%])

Table 14. Transporter substrate restrictions

Transporters	Examples of substrates
OATP1 (B1 or B3)	bosentan, fexofenadine, glyburide, pitavastatin, pravastatin, **repaglinide**, rosuvastatin
MATE (1 or 2K)	cisplatin

Substrates in **bold** type have a narrow therapeutic index.
Reference: Expert Opin. Drug Metab. Toxicol. (2013) 9(6):737-751. Washout period should be 5 times reported terminal half-life.

Appendix 5. Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

INTRODUCTION

This Appendix describes the process to be followed to identify and appropriately report potential Hy's law (PHL) cases and Hy's law (HL) cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study, the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a subject meets PHL criteria at any point during the study. All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits, including central and all local laboratory evaluations, even if collected outside of the study visits (eg, PHL criteria could be met by an elevated ALT from a central laboratory and/or elevated total bilirubin from a local laboratory). The investigator will also review adverse event (AE) data (eg, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The investigator participates with the sponsor in the review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury (DILI) caused by the investigational medicinal product (IMP). The investigator is responsible for recording data pertaining to PHL/HL cases and for reporting AEs and serious adverse events (SAEs) according to the outcome of the review and assessment in line with standard safety-reporting processes.

DEFINITIONS

Potential Hy's Law

AST or ALT ≥3 x ULN together with total bilirubin ≥2 x ULN at any point during the study after the start of study drug, irrespective of an increase in alkaline phosphatase.

Hy's Law

AST or ALT ≥3 x ULN together with total bilirubin ≥2 x ULN, where no reason other than the IMP can be found to explain the combination of increases (eg, elevated alkaline phosphatase indicating cholestasis, viral hepatitis, or another drug).

For PHL and HL, the elevation in transaminases must precede or be coincident with (i.e., on the same day) the elevation in total bilirubin, but there is no specified timeframe within which the elevations in transaminases and total bilirubin must occur.

IDENTIFICATION OF POTENTIAL HY'S LAW CASES

Laboratory data must be comprehensively reviewed by the investigator for each subject to identify laboratory values meeting the following criteria:

- ALT ≥3 x ULN
- AST ≥3 x ULN
- Total bilirubin ≥2 x ULN

When the identification criteria are met from central or local laboratory results, the investigator will perform the following:

- Notify the sponsor representative/Medical Monitor by telephone and report the case as an SAE of Potential Hy's law; seriousness criteria "Important medical event" and causality assessment "yes/related" or in accordance with the clinical study protocol as appropriate.
- Request a repeat of the test (new blood draw) without delay
- Complete the appropriate unscheduled laboratory electronic Case Report Form (eCRF) module(s)
- Perform follow-up on subsequent laboratory results according to the guidance provided in the clinical study protocol, as applicable

REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

The instructions in this section should be followed by the investigator for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality is initially detected, the study Medical Monitor and the Investigator will review available data, to agree whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP and to ensure that timely analysis and reporting to health authorities within 15 calendar days from the date PHL criteria were met.

Where there is an agreed alternative explanation for the ALT or AST and total bilirubin elevations, a determination of whether the alternative explanation is an AE will be made and, subsequently, whether the AE meets the criteria for an SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF.

- If the alternative explanation is an AE/SAE, update the previously submitted PHL SAE accordingly with the new information (reassessing event term, causality, and seriousness criteria) following the sponsor's standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and total bilirubin elevations other than the IMP, then:

- Send updated SAE (report term "Hy's law") according to the sponsor's standard processes:
    - The "Medically Important" serious criterion should be used if no other serious criteria apply.
    - Because there is no alternative explanation for the HL case, a causality assessment of "related" should be assigned.

If there is an unavoidable delay of over 15 calendar days in obtaining the information necessary to assess whether the case meets the criteria for HL, then it is assumed that there is no alternative explanation until an informed decision can be made:

- Provide any further update to the previously submitted SAE of PHL (report term now "Hy's law case"), ensuring causality assessment is related to IMP and seriousness criteria are medically important, according to clinical study protocol process.
- Continue follow-up and review according to the agreed plan. After the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following the clinical study protocol process, according to the outcome of the review.

ACTIONS REQUIRED FOR REPEAT EPISODES OF POTENTIAL HY'S LAW

This section is applicable when a subject meets PHL criteria while receiving study treatment and has already met PHL criteria at a previous on-study treatment visit. The requirement to conduct follow-up, review, and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The investigator should determine the cause for the previous occurrence of PHL and answer the following question:

> Was the alternative cause for the previous occurrence of PHL determined to be the disease under study (eg, chronic or progressing malignant disease, severe infection, or liver disease)?

- If the answer is **No:**

  > Follow the process described in "Potential Hy's Law Criteria Met" in this Appendix for reporting PHL as an SAE.

- If the answer is **Yes**:

  > Determine whether there has been a significant change in the subject's condition compared with the previous occurrence of PHL. Note: A "significant" change in the subject's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or total bilirubin) in isolation or in combination or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator; this may be in consultation with the study medical monitor if there is any uncertainty.
  >
  > - If there is no significant change, no action is required.
  > - If there is a significant change, follow the process described in "Potential Hy's Law Criteria Met" in this Appendix for reporting PHL as an SAE.

LABORATORY TESTS

The list below represents a comprehensive list of follow-up tests that may aid in assessing PHL/HL.

Test results used to assess PHL/HL should be recorded on the appropriate eCRF.

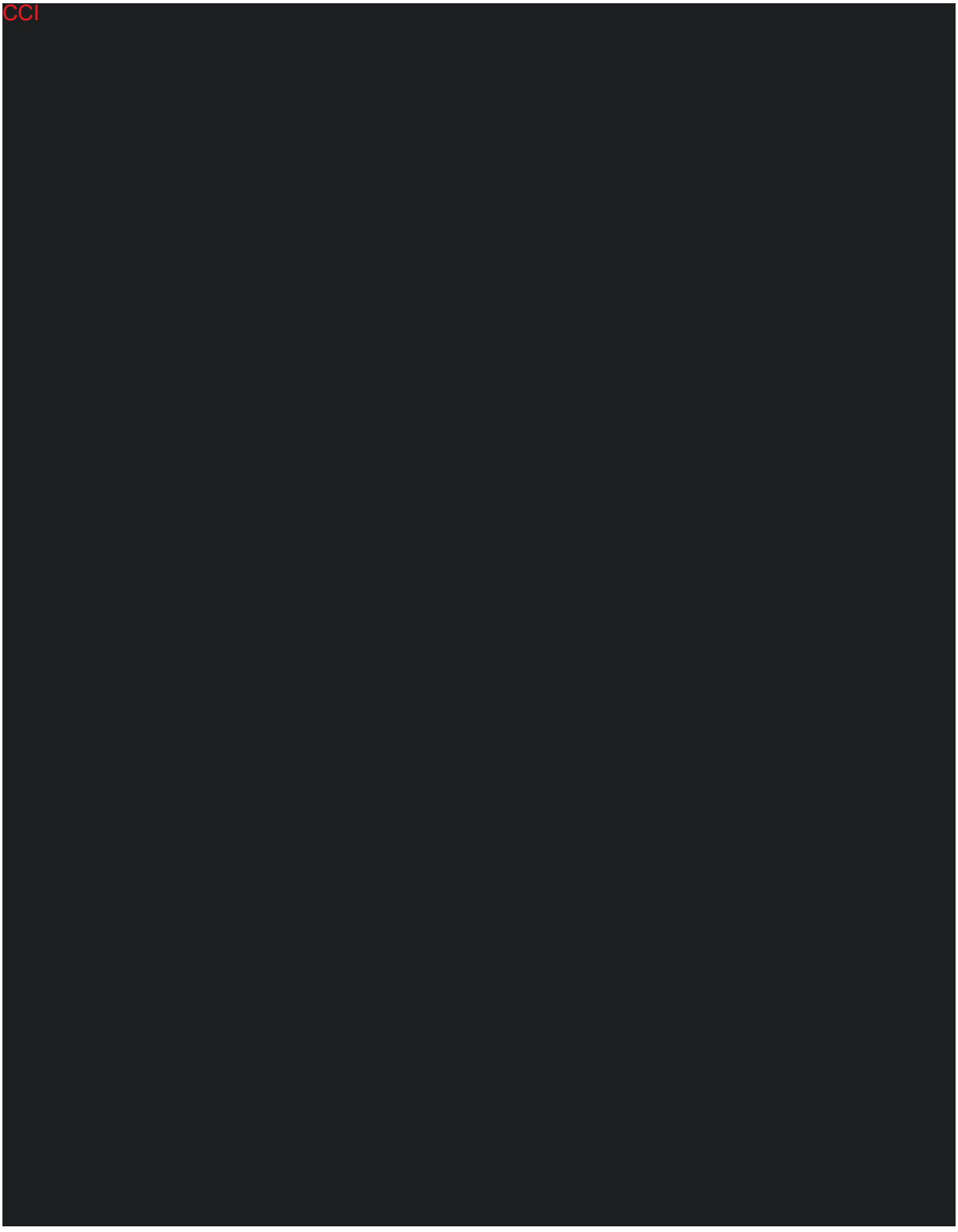
Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV IgM and IgG anti-HBc HBsAg HBV DNA IgM and IgG anti-HCV HCV RNA IgM anti-HEV HEV RNA

Other viral infections	IgM & IgG anti-CMV IgM & IgG anti-HSV IgM & IgG anti-EBV
Alcoholic hepatitis	Carbohydrate deficient transferrin (CD-transferrin)
Autoimmune hepatitis	Antinuclear antibody (ANA) Anti-Liver/Kidney Microsomal Ab (Anti-LKM) Anti-Smooth Muscle Ab (ASMA)
Metabolic diseases	alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin Transferrin saturation

Reference

FDA Guidance for Industry (issued July 2009). Drug-induced liver injury: Premarketing clinical evaluation
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

CCI



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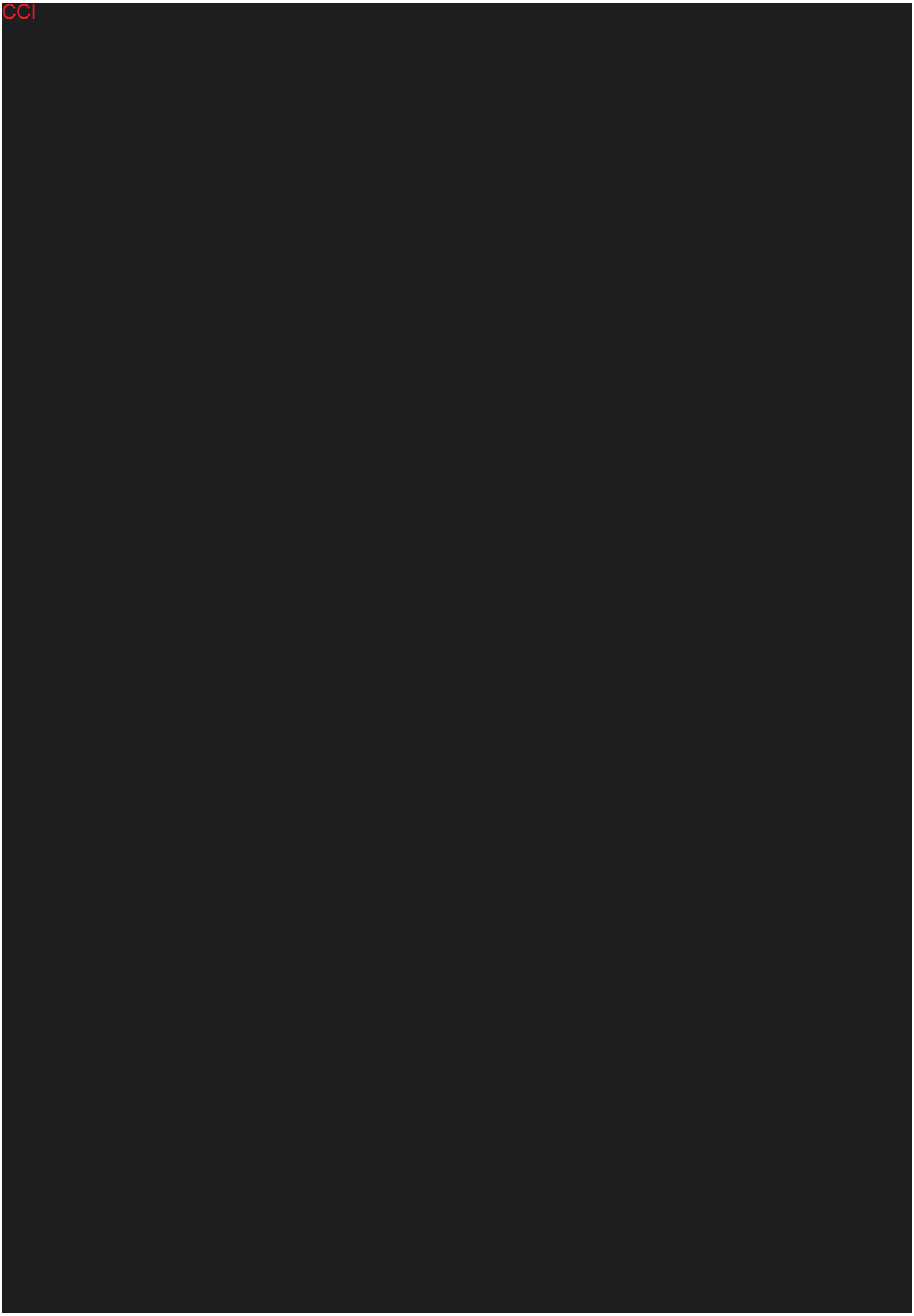

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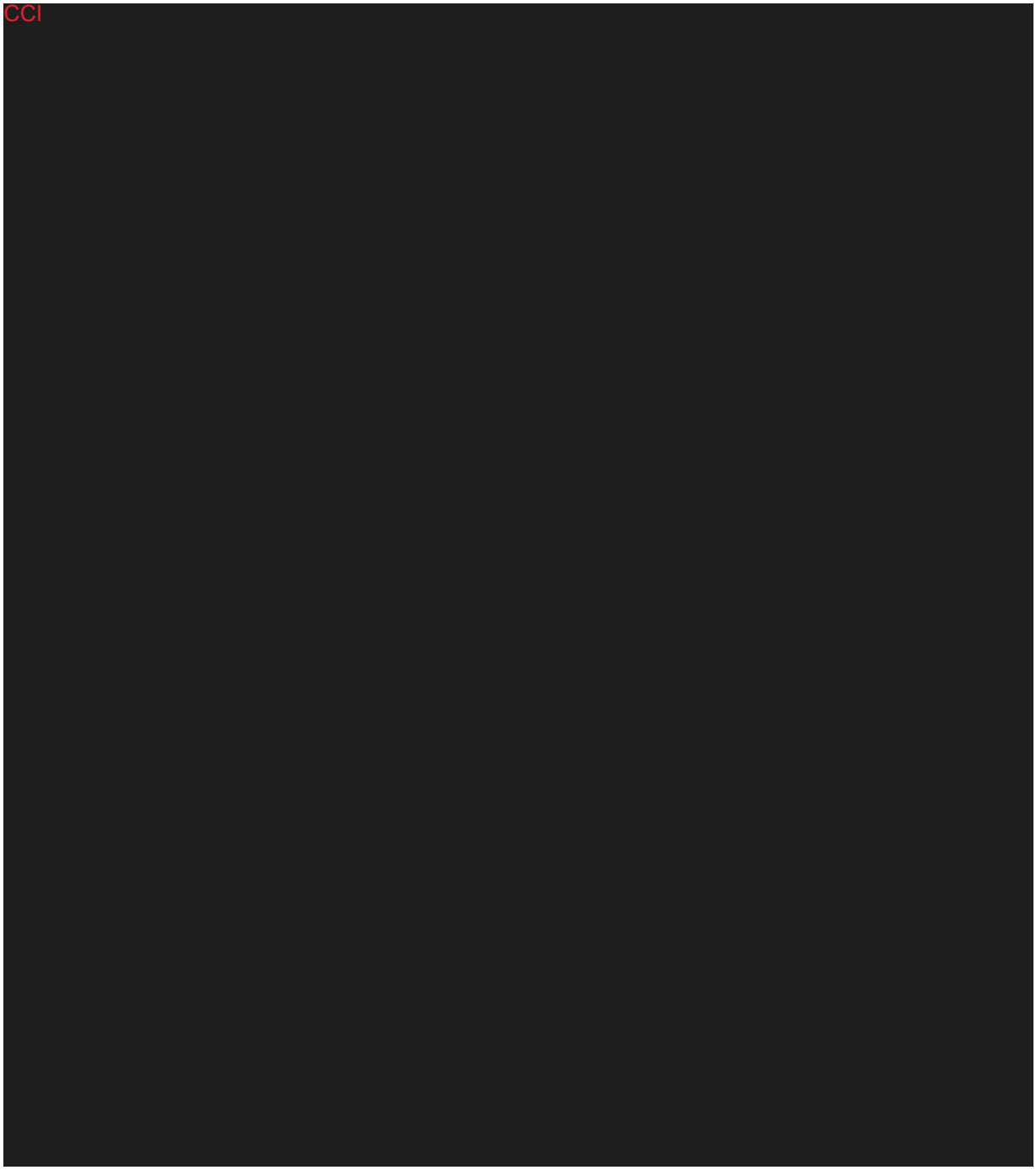

Appendix 7. Cumulative Illness Rating Scale-Geriatric (CIRS-G) Calculator

Web-based CIRS-G calculator link:
http://eforms.moffitt.org/cirsgScore.aspx

SAOP - CIRS-G Score Calculator -redirect - H. Lee Moffitt Cancer Center & Research Institute - H. Lee Moffitt Canc... Page 1 of 1

CIRS-G Score Calculator

*This calculator is based on Miller et al. Cumulative Illness Rating Scale-Geriatric: Miller et al., Psychiatry Res, 41,237-48, 1992.We corrected some discrepancies in the manual and added some comments.***Pubmed ID:** 1594710

* **Please click on each link to view/close help on assigning scores**

Patient: **Age:**

Rater: **Date:** 12/19/2011

Heart Score	0
Vascular Score	0
Hematopoietic Score	0
Respiratory Score	0
Eyes, Ears, Nose, Throat & Larynx	0
Upper GI Score	0
Lower GI Score	0
Liver Score	0
Renal Score	0
Genitourinary Score	0
Musculoskeletal/Integument Score	0
Neurological Score	0
Endocrine/Metabolic & Breast Score	0
Psychiatric Score	0

Rating Malignancies

Unlisted Diseases

Submit

http://www.moffitt.org/Site.aspx?spid=4ACED188A74146C996083374C88849CC&type=cirsgScore 12/29/2011

Appendix 8. Adverse Event Assessment of Causality

Is there a reasonable possibility that the event may have been caused by study drug?

No___ Yes___

The descriptions provided below will help guide the principal investigator in making the decision to choose either “yes” or “no”:

No = There is no reasonable possibility that the event may have been caused by study drug.

The adverse event:

- may be judged to be due to extraneous causes such as disease or environment or toxic factors
- may be judged to be due to the subject’s clinical state or other therapy being administered
- is not biologically plausible
- does not reappear or worsen when study drug is re-administered
- does not follow a temporal sequence from administration of study drug

Yes = There is a reasonable possibility that the event may have been caused by study drug.

The adverse event:

- follows a temporal sequence from administration of study drug
- is a known response to the study drug based on clinical or preclinical data
- could not be explained by the known characteristics of the subject’s clinical state, environmental or toxic factors, or other therapy administered to the subject
- disappears or decreases upon cessation or reduction of dose of study drug
- reappears or worsens when study drug is re-administered

Appendix 9. Response Criteria for NHL

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SPECIAL ARTICLE

Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification

Bruce D. Cheson, Richard I. Fisher, Sally F. Barrington, Franco Cavalli, Lawrence H. Schwartz, Emanuele Zucca, and T. Andrew Lister

See accompanying article on page 3048

A B S T R A C T

Abstract

The purpose of this work was to modernize recommendations for evaluation, staging, and response assessment of patients with Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). A workshop was held at the 11th International Conference on Malignant Lymphoma in Lugano, Switzerland, in June 2011, that included leading hematologists, oncologists, radiation oncologists, pathologists, radiologists, and nuclear medicine physicians, representing major international lymphoma clinical trials groups and cancer centers. Clinical and imaging subcommittees presented their conclusions at a subsequent workshop at the 12th International Conference on Malignant Lymphoma, leading to revised criteria for staging and of the International Working Group Guidelines of 2007 for response. As a result, fluorodeoxyglucose (FDG) positron emission tomography (PET)–computed tomography (CT) was formally incorporated into standard staging for FDG-avid lymphomas. A modification of the Ann Arbor descriptive terminology will be used for anatomic distribution of disease extent, but the suffixes A or B for symptoms will only be included for HL. A bone marrow biopsy is no longer indicated for the routine staging of HL and most diffuse large B-cell lymphomas. However, regardless of stage, general practice is to treat patients based on limited (stages I and II, nonbulky) or advanced (stage III or IV) disease, with stage II bulky disease considered as limited or advanced disease based on histology and a number of prognostic factors. PET-CT will be used to assess response in FDG-avid histologies using the 5-point scale. The product of the perpendicular diameters of a single node can be used to identify progressive disease. Routine surveillance scans are discouraged. These recommendations should improve evaluation of patients with lymphoma and enhance the ability to compare outcomes of clinical trials.

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0732-183X/14/3227w-3059w/$20.00

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INTRODUCTION

The availability of more effective therapies for lymphoma and the increasingly sensitive and specific technologies for disease assessment provide rationale for updated patient evaluation, staging, and response criteria. These should be unambiguous and universally applicable and facilitate the comparison of patients and results among studies and the evaluation of new therapies by regulatory agencies.

Staging defines disease location and extent, suggests prognostic information, allows comparisons among studies, and provides a baseline against which response or disease progression can be compared. Initial staging criteria were designed primarily for Hodgkin lymphoma (HL)[1-3] and were superseded by the Ann Arbor classification,[4] which subdivided HL patients into four stages and subclassification A and B based on the presence of fevers to greater than 101°F (38.3°C), weight loss, and night sweats and which has been the most widely used classification since its introduction. The Cotswold classification[5] first formally incorporated computed tomography (CT) scans and introduced "X" for bulky disease and complete remission unconfirmed (CRu) to describe patients with a residual mass after treatment that was most likely fibrous tissue.

The first universally accepted response criteria for non-Hodgkin lymphoma (NHL), used also for HL, were published in 1999 by the National Cancer Institute Working Group[6] and revised in 2007 by the International Working Group (IWG)[7] to incorporate positron emission tomography (PET) and bone marrow immunohistochemistry and flow cytometry in response assessment, eliminating CRu.

Table 1. Criteria for Involvement of Site

Tissue Site	Clinical	FDG Avidity	Test	Positive Finding
Lymph nodes	Palpable	FDG-avid histologies	PET-CT	Increased FDG uptake
		Nonavid disease	CT	Unexplained node enlargement
Spleen	Palpable	FDG-avid histologies	PET-CT	Diffuse uptake, solitary mass, miliary lesions, nodules
		Nonavid disease	CT	> 13 cm in vertical length, mass, nodules
Liver	Palpable	FDG-avid histologies	PET-CT	Diffuse uptake, mass
		Nonavid disease	CT	Nodules
CNS	Signs, symptoms		CT	Mass lesion(s)
			MRI	Leptomeningeal infiltration, mass lesions
			CSF assessment	Cytology, flow cytometry
Other (eg, skin, lung, GI tract, bone, bone marrow)	Site dependent		PET-CT*, biopsy	Lymphoma involvement

Abbreviations: CSF, cerebrospinal fluid; CT, computed tomography; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography.
*PET-CT is adequate for determination of bone marrow involvement and can be considered highly suggestive for involvement of other extralymphatic sites. Biopsy confirmation of those sites can be considered if necessary.

After extensive experience with these criteria, and recognizing the progress made after their publication, particularly in imaging techniques, a workshop was held at the 11th International Conference on Malignant Lymphoma in Lugano, Switzerland, in June 2011, which was attended by leading hematologists, oncologists, radiation oncologists, pathologists, radiologists, and nuclear medicine physicians, representing major lymphoma clinical trials groups and cancer centers in North America, Europe, Japan, and Australasia. The aim was to develop improved staging and response criteria for HL and NHL, relevant for community physicians, investigator-led trials, cooperative groups, and registration trials. Subcommittees focused on clinical and imaging issues, and a subsequent workshop at the 12th International Conference on Malignant Lymphoma in 2013 led to the following revisions.

INITIAL EVALUATION

Diagnosis

Lymphoma diagnosis depends on morphology, immunohistochemistry, and flow cytometry reviewed by an experienced lymphoma pathologist and, where appropriate, molecular studies to accurately categorize the lymphoma.[8] A fine-needle aspirate is inadequate for initial diagnosis. An incisional or excisional biopsy is preferred to provide adequate tissue for these examinations, but a core-needle biopsy can be considered when excisional biopsy is not possible[9,10] and to document relapse; however, a nondiagnostic sample must be followed by an incisional or excisional biopsy. With consent, additional paraffin-embedded, fresh-frozen tissue, or cell suspensions should be stored for future research.

Patient Evaluation

Clinical evaluation requires a comprehensive history including age; sex; absence/presence of fevers to more than 101°F (38.3°C), chills, drenching night sweats, or unexplained weight loss more than 10% of body mass over 6 months; and history of malignancy. Fatigue, pruritus, and alcohol-induced pain in patients with HL should also be noted. Whereas these factors rarely direct treatment, their recurrence may herald disease relapse.

Physical examination includes measurement of accessible nodal groups and the size of the spleen and liver in centimeters below their respective costal margins in the midclavicular line. However, the sensitivity of physical examination is variable among observers. Therefore, organomegaly is formally defined by CT imaging (Table 1).

Laboratory tests and other investigations necessary for the determination of the prognostic indices for the different lymphoma subtypes and general patient management, including assessment of comorbidities, must be recorded.

Anatomic Staging

Historical series and prospective clinical trials have used the Ann Arbor staging system[5] to select patients and report outcomes. Now, stage is only one component of factors in prognostic indices increasingly used for pretreatment risk stratification and selection of therapy.[11-15]

PET-CT scanning has become the standard for assessment of response in most lymphomas.[7] For HL and fluorodeoxyglucose (FDG) -avid NHL subtypes, PET and PET-CT improve the accuracy of staging compared with CT scans for nodal and extranodal sites.[16] PET-CT leads to change in stage in 10% to 30% of patients, more often upstaging, although alteration in management occurs in fewer patients, with no demonstrated impact on overall outcome. However, improving staging accuracy ensures that fewer patients are undertreated or overtreated.[16] PET-CT is particularly important for staging before consideration of radiation therapy.[17,18] Although most lymphomas are FDG avid, because of greater variability in FDG uptake, metabolic imaging is less reliable in other lymphomas.[19-24] Whereas mantle-cell lymphoma is routinely FDG avid, limited data suggest that the sensitivity and specificity of identifying bowel involvement are low and should not replace other investigative measures.[25,26]

RECOMMENDATION FOR REVISIONS TO STAGING CRITERIA

PET-CT is already widely used for pretreatment assessment, often outside of clinical trials, to assign stage and has already been incorporated into response assessment.[7] Although physical examination remains important, and despite concerns that more sensitive staging can

result in stage migration, impairing the use of historically controlled data, PET-CT is critical as a baseline measurement before therapy to increase the accuracy of subsequent response assessment[27,28] (Table 1). Therefore, the consensus was that PET-CT should be recommended for routine staging of FDG-avid, nodal lymphomas (essentially all histologies except chronic lymphocytic leukemia/small lymphocytic lymphoma, lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia, mycosis fungoides, and marginal zone NHLs, unless there is a suspicion of aggressive transformation) as the gold standard.[24]

The following recommendations are intended for lymphomas with primarily nodal involvement, although they are also applicable to primary extranodal diffuse large B-cell lymphoma (DLBCL). Separate criteria have been proposed for primary extranodal[29,30] and cutaneous lymphomas.[31]

Imaging

PET-CT is preferred for staging of FDG-avid lymphomas, and CT scan is preferred in the other lymphomas. A chest x-ray is no longer required in lymphoma staging because it less accurate than CT.[32] Moreover, CT identifies more hilar nodes and may better discriminate between a single large nodal mass and an aggregate of individual nodes. Bulk is a negative prognostic factor,[11,13-15] but there is little agreement on its definition, which is disease, stage, and treatment specific.

These criteria strongly recommend PET-CT for staging of routinely FDG-avid histologies, especially in clinical trials. A contrast-enhanced CT scan should be included for a more accurate measurement of nodal size if required for trials; if necessary, to more accurately distinguish bowel from lymphadenopathy; and in the setting of compression/thrombosis of central/mediastinal vessels. Contrast-enhanced CT is also preferred for radiation planning. Variably FDG-avid histologies should be staged with a CT scan.

For patients staged with PET-CT, focal uptake in nodal and extranodal sites that is in keeping with lymphoma, according to the distribution and/or CT characteristics, is considered involvement with lymphoma, including spleen, liver, bone, thyroid, and so on. For patients staged with CT, up to six of the largest target nodes, nodal masses, or other lymphomatous lesions that are measurable in two diameters (longest diameter [LDi] and shortest diameter) should be identified from different body regions representative of the patient's overall disease burden and include mediastinal and retroperitoneal disease, if involved. A measurable node must have an LDi greater than 1.5 cm. Measurable extranodal disease (eg, hepatic nodules) may be included in the six representative, measured lesions. A measurable extranodal lesion should have an LDi greater than 1.0 cm. All other lesions (including nodal, extranodal, and assessable disease) should be followed as nonmeasured disease (eg, cutaneous, GI, bone, spleen, liver, kidneys, pleural or pericardial effusions, ascites). In patients in whom a discordant histology or malignant transformation is suspected, a PET-CT may identify the optimal site to biopsy for confirmation.[20,21]

Tumor Bulk

A single nodal mass, in contrast to multiple smaller nodes, of 10 cm or greater than a third of the transthoracic diameter at any level of thoracic vertebrae as determined by CT is retained as the definition of bulky disease for HL.[5] A chest x-ray is not required to determine bulk because of its high concordance with CT.[32] However, a variety of sizes have been suggested for NHL,[15,33] with limited evidence suggesting 6 cm as best for follicular lymphoma[15] and 6 to 10 cm in the rituximab era for DLBCL.[34] However, none of the proposed sizes have been validated in the current therapeutic era. Therefore, the recommendation for HL and NHL is to record the longest measurement by CT scan, with the term X no longer necessary.

Spleen Involvement

A wide range of normal spleen sizes has been reported,[35-37] related to race, body size, and height.[38] A spleen may be of normal size and still contain lymphoma or may be enlarged as a result of variations in blood volume, use of hematopoietic growth factors, or lymphoma-unrelated causes. Splenic involvement is best determined by PET-CT and may be characterized by homogeneous splenomegaly, diffuse infiltration with miliary lesions, focal nodular lesions, or a large solitary mass.[39] There is no agreement on whether single, multiple, or volumetric measurements should be used to measure spleen size[35] or what cutoff to use for splenomegaly. For simplicity, a single measurement that correlates well with volume[40,41] is preferable to a volumetric measurement or estimation by equations, with special software, which are unlikely to be used routinely.

Most studies use 10 to 12 cm for vertical length. Our recommendation is to use a cutoff for splenomegaly of more than 13 cm.

Liver Involvement

Given variability in body habitus and the impact of numerous medical conditions, liver size by physical examination or CT scan is not a reliable measure of hepatic involvement by lymphoma. Similar to splenic involvement, diffusely increased or focal uptake, with or without focal or disseminated nodules, supports liver involvement.

Bone Marrow Involvement

Bone marrow biopsy (BMB) has been standard in lymphoma staging,[5] although it is often performed even when the likelihood of involvement is low. The high sensitivity of PET-CT for bone marrow involvement has recently called into question the continued use of BMB in several common histologies.[42-46] In one study in HL, 18% of patients had focal skeletal lesions on PET-CT, but only 6% had positive BMB,[46] all with advanced disease on PET-CT. None of the patients would have been allocated to another treatment based on BMB results. Patients with early-stage disease rarely have involvement in the absence of a suggestive PET finding, and those with advanced-stage disease rarely have involvement in the absence of disease-related symptoms or other evidence of advanced-stage disease. Thus, if a PET-CT is performed, a bone marrow aspirate/biopsy is no longer required for the routine evaluation of patients with HL.

In DLBCL, PET-CT is also more sensitive than BMB but has been reported to miss low-volume diffuse involvement of 10% to 20% of the marrow.[42,47-49] Nevertheless, patients with clinical early-stage disease rarely have involvement in the absence of a suggestive PET finding. In one study in DLBCL, 27% of patients were found to have marrow involvement (94% by PET-CT and only 40% by BMB). BMB was negative in 21 of 28 patients with focal disease on PET-CT and did not upstage any patients. Two cases (1.5%) of bone marrow involvement went undetected by PET-CT, with a 10% infiltrate of large cells. Thus, a PET-CT scan indicating bone or marrow involvement is

usually sufficient to designate advanced-stage disease, and a BMB is not required. Patients with a positive BMB generally have other factors consistent with advanced stage or poor prognosis.[49,50] If the scan is negative, a BMB is indicated to identify involvement by discordant histology if relevant for a clinical trial or patient management.[51]

The data in all other lymphoma histologies are insufficient to change the standard practice, and a 2.5-cm unilateral BMB is recommended, along with immunohistochemistry and flow cytometry.

PROGNOSTIC GROUPS AND TREATMENT ALLOCATION

The increased use of systemic and multimodality approaches has made Ann Arbor stage less relevant in directing the choice of therapy. Nevertheless, we recommend a modification of the Ann Arbor classification (Table 2) for anatomic description of disease extent. However, regardless of stage, general practice is to treat patients based on limited (stages I and II, nonbulky) or advanced (stages III or IV) disease, with stage II bulky disease considered limited or advanced as determined by histology and a number of prognostic factors. The designation E for extranodal disease is relevant only for limited extranodal disease in the absence of nodal involvement (IE) or in patients with stage II disease and direct extension to a non-nodal site. E is not relevant to patients with advanced-stage disease.

The Ann Arbor classification subdivides patients according to the absence (A) or presence (B) of disease-related symptoms. However, these features are frequently neither recorded nor accurate. Moreover, in the International Prognostic Index,[12] Follicular Lymphoma International Prognostic Index,[13] Follicular Lymphoma International Prognostic Index 2,[15] Mantle Cell International Prognostic Index,[14] and International Prognostic Score,[11] constitutional symptoms do not confer an unfavorable outcome. Thus, only patients with HL need be assigned the designations A or B because symptoms only direct treatment in that disease.

Table 2. Revised Staging System for Primary Nodal Lymphomas

Stage	Involvement	Extranodal (E) Status
Limited		
I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
II bulky*	II as above with "bulky" disease	Not applicable
Advanced		
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
IV	Additional noncontiguous extralymphatic involvement	Not applicable

NOTE. Extent of disease is determined by positron emission tomography–computed tomography for avid lymphomas and computed tomography for nonavid histologies. Tonsils, Waldeyer's ring, and spleen are considered nodal tissue.

*Whether stage II bulky disease is treated as limited or advanced disease may be determined by histology and a number of prognostic factors.

Summary

Excisional biopsy is preferred for diagnosis, although core-needle biopsy may suffice when not feasible.

Clinical evaluation includes careful history, relevant laboratory tests, and recording of disease-related symptoms.

PET-CT is the standard for FDG-avid lymphomas, whereas CT is indicated for nonavid histologies.

A modified Ann Arbor staging system is recommended; however, patients are treated according to prognostic and risk factors.

Suffixes A and B are only required for HL.

The designation X for bulky disease is no longer necessary; instead, a recording of the largest tumor diameter is required.

If a PET-CT is performed, a BMB is no longer indicated for HL; a BMB is only needed for DLBCL if the PET is negative and identifying a discordant histology is important for patient management.

ASSESSMENT OF RESPONSE AFTER TREATMENT

End-of-treatment assessment is more accurate with PET-CT, especially for patients with radiologic (CT) CRu or partial response (PR) in HL, DLBCL, and follicular lymphoma.[7,52-55] PET-CT–based criteria eliminate CRu and improve the prognostic value of PR. In early- and advanced-stage patients with HL, a negative predictive value of 95% to 100% and positive predictive value of more than 90% have been reported.[56,57] In aggressive NHL, studies have reported a negative predictive value of 80% to 100% but a lower positive predictive value, ranging from 50% to 100%.[58-61] If further treatment based on residual metabolically active disease on PET-CT is being considered, either biopsy or follow-up scan is advised. In these lymphoma subtypes, response assessment with PET-CT may be preferred.

The IWG criteria for reviewing PET scans were based on visual interpretation and intended for end-of-treatment evaluation,[62] using mediastinal blood pool as the comparator. The current recommendation is to use the 5-point scale, both for clinical trials including interim analysis and for end-of-treatment assessment (Table 3).[24] Interim PET-CT is used to assess early treatment response and, at end of treatment, to establish remission status. A score of 1 or 2 is considered to represent complete metabolic response at interim and end of treatment. FDG uptake declines during therapy in chemotherapy-sensitive disease, and residual FDG uptake higher than normal liver uptake is frequently seen at interim in patients who achieve complete metabolic response at the end of treatment. More recent data also suggest that most patients with uptake higher than mediastinum but less than or equivalent to liver (score of 3) have good prognosis at the end of treatment with standard therapy in HL,[63] DLBCL,[61] and follicular lymphoma.[54] However, in response-adapted trials exploring treatment de-escalation, a more cautious approach may be preferred, judging a score of 3 to be an inadequate response to avoid undertreatment. Therefore, interpretation of a score of 3 depends on the timing of assessment, the clinical context, and the treatment. A score of 4 or 5 at interim suggests chemotherapy-sensitive disease, provided uptake has reduced from baseline, and is considered to represent partial metabolic response. At the end of treatment, residual metabolic disease with a score of 4 or 5 represents treatment failure even if uptake has reduced from baseline. A score of 4 or 5 with intensity that does not change or even increases from baseline and/or new foci compatible

with lymphoma represents treatment failure at interim and at the end-of-treatment assessment.

In most cases, lack of significant response can be interpreted visually. Although ideally a quantitative cutoff might improve consistency, there is insufficient evidence to quantify precisely the reduction in uptake that predicts adequate response using FDG-PET for lymphoma, which is dependent on disease type, timing, and treatment given. Recent data suggest that the CT scan may play a complimentary role in patients with HL who have either a positive interim or post-treatment PET-CT, with a greater reduction in tumor mass correlating with an improved outcome.[64,65] How best to use this information remains to be determined.

CT-based response is preferred for histologies with low or variable FDG avidity and in regions of the world where PET-CT is unavailable. However, in the absence of a PET-CT scan, a mass that has decreased in size but persists is considered at best a PR in the absence of biopsy documenting absence of lymphoma, and the former term CRu is not to be considered.[7] In trials exploring new agents in multiply relapsed disease where data are lacking regarding PET-CT and where assessment of disease control is more important than likelihood of cure, CT-based response may also be more relevant (Table 3).

At interim or end of therapy, tests that were abnormal before treatment should be repeated, including assessment of extranodal sites. Response assessment is detailed in Table 3 and in the following sections.

Nodes or Extranodal Lesions That Split When Disease Is Responding

If a confluent nodal mass splits into several discrete nodes, the individual product of the perpendicular diameters (PPDs) of the nodes should be summed together to represent the PPD of the split lesion; this PPD is added to the sum of the PPDs of the remaining lesions to measure response. If subsequent growth of any or all of these discrete nodes occurs, the nadir of each individual node is used to determine progression (as if each individual node was selected as a target lesion at baseline).

Nodes or Extranodal Lesions That Become Confluent When Disease Is Progressing

If a group of target lymph nodes becomes confluent, the PPD of the current confluent mass should be compared with the sum of the PPDs of the individual nodes, with more than 50% increase in the PPD of the confluent mass compared with the sum of individual nodes necessary to indicate progressive disease. The LDi and shortest diameter are no longer needed to determine progression.

Additional Response Assessment Guidelines

The presence of residual symptoms in the absence of detectable disease by imaging does not preclude the designation CR. In the context of an agent associated with a flare reaction, caution must be exercised not to confuse the possible tumor flare with progressive disease. It is recommended that either a biopsy be performed or the lesion be reassessed in at least 2 weeks, and if there is continued evidence of tumor progression, the date of progressive disease is the previous evaluation.

FOLLOW-UP EVALUATIONS

Good clinical judgment, a careful history, and physical examination are the cornerstones of patient follow-up. The IWG, National Comprehensive Cancer Network, and European Society for Medical Oncology published recommendations for follow-up that vary by histology (curable *v* incurable), whether a patient is on a clinical trial or managed with standard of care, or the clinical setting (eg, initial *v* relapsed/refractory disease; complete response *v* PR to treatment).[7,66,67] For example, for curable histologies such as HL and DLBCL, the likelihood of relapse decreases over time; thus, the frequency of follow-up should decrease, with visits being reduced from every 3 months during the first 2 years, to every 6 months for the next 3 years, and then annually thereafter to monitor for late relapse and treatment-related adverse effects. In contrast, in follicular lymphoma, mantle-cell lymphoma, and other incurable histologies, the likelihood of recurrence continues or increases over time, and patients should be observed every 3 to 6 months, determined by pretreatment risk factors, whether the patient is being managed conservatively, and whether treatment has achieved a complete or less than complete response. In addition, a CBC, metabolic panel, and serum lactate dehydrogenase are recommended.

Published studies fail to support routine surveillance scans, and they are discouraged.[68-70] The false-positive rate with PET scans is greater than 20%, leading to unnecessary investigations, radiation exposure, biopsies, expense, and patient anxiety. Follow-up scans should be prompted by clinical indications. In clinical trials with time-dependent end points (eg, progression-free survival, event-free survival), a CT scan is determined by the study-designated interval. In the indolent lymphomas, asymptomatic intra-abdominal or retroperitoneal disease progression may be a concern in patients with residual disease in those areas after therapy. In such patients, judicious use of scans can be considered. In clinical practice and in clinical trials, attempts should be made to limit the number of scans to which a patient is exposed.

Summary

PET-CT should be used for response assessment in FDG-avid histologies, using the 5-point scale; CT is preferred for low or variable FDG avidity.

A complete metabolic response even with a persistent mass is considered a complete remission.

A PR requires a decrease by more than 50% in the sum of the product of the perpendicular diameters of up to six representative nodes or extranodal lesions.

Progressive disease by CT criteria only requires an increase in the PPDs of a single node by $\geq$ 50%.

Surveillance scans after remission are discouraged, especially for DLBCL and HL, although a repeat study may be considered after an equivocal finding after treatment.

Judicious use of follow-up scans may be considered in indolent lymphomas with residual intra-abdominal or retroperitoneal disease.

MEASUREMENT OF OUTCOME

Definitions are consistent with the IWG definitions.[7]

Table 3. Revised Criteria for Response Assessment

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS†	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions

(continued on following page)

Table 3. Revised Criteria for Response Assessment (continued)

Response and Site	PET-CT–Based Response	CT-Based Response
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

†PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

CONCLUDING REMARKS

Accurate pretreatment evaluation and response assessment are critical to the optimal management of patients with lymphoma. With increasing knowledge of the disease, new prognostic factors, and a better understanding of tumor biology comes a need to update prior systems. Despite the importance of a physical examination, imaging studies have become the standard. The present recommendations are directed primarily at initial staging and assessment, and their role in the multiply relapsed setting and early clinical trials remains to be confirmed. A major departure from the Ann Arbor system and the IWG criteria is that PET-CT is included in staging for FDG-avid lymphomas, because it is more sensitive than CT and provides a baseline against which response is more accurately assessed. Patients should be treated based on prognostic factors. Subclassification of A and B is now only indicated if prognostically important (ie, HL). Patients, including those with HL and most with DLBCL, can be spared a staging BMB,[71] and a routine chest x-ray is unnecessary for staging, although it may be useful for monitoring select patients with HL. Although the current definition of bulk is retained for HL, further correlations between maximum tumor diameter and outcome are needed to provide a clinically meaningful definition of bulk with current treatment approaches for NHL. Response assessment is preferred for FDG-avid lymphomas where possible, using the 5-point scale, whereas CT-based response remains important in lymphomas with low or variable FDG avidity, and in multiply relapsed disease, CT criteria for progressive disease can be based on an increase of a single lesion. The better we are able to exploit the biology of lymphomas for therapeutic benefit, the more our treatment strategies will be determined by relevant receptors and pathways, with even less reliance on Ann Arbor staging. Hopefully, the current recommendations will provide the necessary standardization of clinical trial conduct and interpretation that leads to improved therapies for patients with lymphoma.

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