Official Protocol Title:	A Phase IB Trial with MK-8628, a Small Molecule Inhibitor of the Bromodomain and Extra-Terminal (BET) Proteins, in Subjects with Selected Hematologic Malignancies
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SPONSOR:
Oncoethix GmbH, a wholly owned subsidiary of Merck Sharp & Dohme Corp. (hereafter referred to as the Sponsor or Merck)
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TITLE:

A Phase IB Trial with MK-8628, a Small Molecule Inhibitor of the Bromodomain and Extra-Terminal (BET) Proteins, in Subjects with Selected Hematologic Malignancies

IND NUMBER: 116,806
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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
All	All	Enrollment in this protocol was prematurely discontinued due to the Sponsor's decision to terminate the MK-8628 program based on very limited efficacy signals and evaluation of the risk/benefit profile given limited efficacy. It is important to note that this program was not being discontinued due to a safety concern with MK-8628. Previous procedures are not deleted from this amendment but are superseded by this amendment. This is outlined in the Summary of Changes. Upon approval of this amendment by the site's Institutional Review Board (IRB) or Independent Ethics Committee (IEC), data entry in the data entry system eCRF will no longer be required, the database will be closed, and procedures and the outcome of procedures should be documented in the medical record. The IVRS was closed after the last subject was enrolled, and trial site personnel will contact the Sponsor 3 weeks before additional clinical supplies are required to treat the remaining subject. Continued treatment is subject to availability of study medications. Procedures as detailed in MK-8628-005-02 will be performed as standard of care.	To allow the remaining subject enrolled in the trial to continue to receive treatment with MK-8628.

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
		No efficacy measures will be recorded. Imaging studies will be conducted only to determine the subject's response to treatment. All serious adverse events will be reported to the Sponsor's central safety reporting system using the paper reporting method as outlined in the Investigator trial file.	
1.0	Trial Summary	*Added statements at the beginning of the section.* Enrollment in this protocol was prematurely discontinued due to the Sponsor's decision to terminate the MK-8628 program based on very limited efficacy signals and evaluation of the risk/benefit profile given limited efficacy. It is important to note that this program was not being discontinued due to a safety concern with MK-8628. Previous procedures are not deleted from this amendment but are superseded by this amendment. This is outlined in the Summary of Changes. Upon approval of this amendment by the site's Institutional Review Board (IRB) or Independent Ethics Committee (IEC), data entry in the data entry system eCRF will no longer be required, the database will be closed, and procedures and the outcome of procedures should be documented in the medical record. The IVRS was closed after the last subject was enrolled, and trial site personnel will contact the	To allow the remaining subject enrolled in the trial to continue to receive treatment with MK-8628.

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		Sponsor 3 weeks before additional clinical supplies are required to treat the remaining subject. Continued treatment is subject to availability of study medications. Procedures as detailed in MK-8628-005-02 will be performed as standard of care. No efficacy measures will be recorded. Imaging studies will be conducted only to determine the subject's response to trial treatment. All serious adverse events will be reported to the Sponsor's central safety reporting system using the paper reporting method as outlined in the Investigator trial file.	

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

No additional changes.

1.0 TRIAL SUMMARY

Enrollment in this protocol was prematurely discontinued due to the Sponsor's decision to terminate the MK-8628 program based on very limited efficacy signals and evaluation of the risk/benefit profile given limited efficacy. It is important to note that this program was not being discontinued due to a safety concern with MK-8628.

Previous procedures are not deleted from this amendment but are superseded by this amendment. This is outlined in the Summary of Changes.

Upon approval of this amendment by the site's Institutional Review Board (IRB) or Independent Ethics Committee (IEC), data entry in the data entry system eCRF will no longer be required, the database will be closed, and procedures and the outcome of procedures should be documented in the medical record. The IVRS was closed after the last subject was enrolled, and trial site personnel will contact the Sponsor 3 weeks before additional clinical supplies are required to treat the remaining subject.

Continued treatment is subject to availability of study medications.

Procedures as detailed in MK-8628-005-02 will be performed as standard of care.

No efficacy measures will be recorded. Imaging studies will be conducted only to determine the subject's response to trial treatment.

All serious adverse events will be reported to the Sponsor's central safety reporting system using the paper reporting method as outlined in the Investigator trial file.

Abbreviated Title	A phase Ib trial with MK-8628, a small molecule inhibitor of the bromodomain and extra-terminal (BET) proteins, in subjects with selected hematologic malignancies.
Sponsor Product Identifiers	MK-8628
Trial Phase	Phase Ib
Clinical Indication	The treatment of subjects with one of the following hematologic malignancies: • Acute myeloid leukemia (AML) - AML de Novo and post-MDS • Diffuse large B cell lymphoma (DLBCL)
Trial Type	Interventional
Type of control	No treatment control
Route of administration	Oral
Trial Blinding	Unblinded Open-label
Treatment Groups	MK-8628 20 mg, twice a day, continuous for 21 consecutive days per cycle; MK-8628 30 mg, twice a day, continuous for 21 consecutive days per cycle
Number of trial subjects	Approximately a maximum of 56 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 20 months from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.

Duration of Participation	Each subject will participate in the trial from the time the subject signs the Informed Consent Form (ICF) through the final contact. After a screening phase of up to 2 weeks, eligible subjects will receive treatment according to their assigned regimen and dose level in 3-week dosing cycles. Treatment with MK-8628 will continue until documented disease progression, unacceptable toxicity, subject withdrawal of consent, subject non-compliance with trial treatment or procedure requirements, treatment interruption > 2 weeks for any reason (except in the event of perceived benefit, with Sponsor agreement), recurrence of dose limiting toxicity (DLT) despite dose reduction (except in the event of perceived benefit, with Sponsor agreement), or by the investigators decision to withdraw the subject. After the end of treatment, subjects are to be followed up for safety for at least 30 days following the last MK-8628 dosing and until recovery or stabilization of all related toxicities.

A list of abbreviations used in this document can be found in Section 12.9.

2.0 TRIAL DESIGN

2.1 Trial Design

This is an open-label, multicenter, international, non-randomized phase Ib trial with dose exploration of single-agent MK-8628 (formally known as OTX015) administered orally in subjects with selected hematologic malignancies (AML and DLBCL), to be conducted in conformance with Good Clinical Practices.

This dose escalation study will evaluate a twice-daily (BID) dosing regimen to establish the recommended phase 2 dose (RP2D).

Dose administration will be continuous for 21 consecutive days per cycle (21-day cycles) at a starting dose of 20 mg BID.

A 6+8 two-stage design is used, offering a fast approach with continuous dose-limiting toxicity (DLT) rate monitoring via a modified toxicity probability index (mTPI)(Ji design) [1]. Two dose levels will be evaluated: 20 and 30 mg BID, continuous, 21-day cycles.

Between 6 and 14 subjects will be enrolled per dose level and per cohort, depending on the occurrence of a DLT (see Sections 5.2.1.2 and 5.2.1.3) during the first 21 days of treatment. Thus a maximum of up to 56 subjects (28 subjects per cohort) evaluable for DLT will be enrolled. All AML subjects participating in the 20 mg BID regimen of the MK-8628-001 protocol (approximately up to 3 subjects) will count toward the initial 6 AML subjects needed for the 20 mg BID dose level in this study.

Subjects will undergo a dose and/or schedule modification in the event of toxicity (see Section 5.2.1).

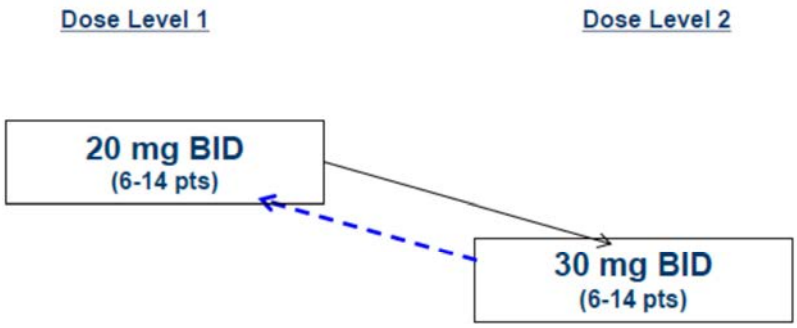
Each cohort (AML and DLBCL) will be evaluated independently in regards to enrollment and dose level escalation/de-escalation.

The RP2D will be selected based on a multi-faceted decision taking into account safety, tolerability, early efficacy signal, PK exposure and PD markers. The primary endpoint driving dose selection is the DLT rate, with weight given to the highest DL tolerated (< 25% DLT rate).

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

2.2 Trial Diagram

The trial design is depicted in Figure 1.



Ji Y, Wang SJ. Modified toxicity probability interval design: a safer and more reliable method than the 3 + 3 design for practical phase I trials. J Clin Oncol. 2013;31(14):1785-91.

Figure 1 Dose Escalation Scheme

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

Objectives for this trial are to be evaluated for single agent MK-8628 administered orally to subjects with selected hematologic malignancies as follows:

1) **Objective**: To determine the recommended phase II dose (RP2D) respectively in subjects with AML and DLBCL.

3.2 Secondary Objective(s) & Hypothesis(es)

Objectives for this trial are to be evaluated for single agent MK-8628 administered orally to subjects with selected hematologic malignancies as follows:

1) **Objective**: To assess the safety and tolerability.
2) **Objective**: To characterize pharmacokinetic (4.2.3.2) and pharmacodynamic (4.2.3.3) parameters.
3) **Objective**: To evaluate antitumor activity using objective response rate (ORR), duration of response (DOR) and disease control rate (DCR) by Response Evaluation Criteria in AML or DLBCL (see Section 7.1.2.7.1 and 7.1.2.7.2) as assessed by investigator review

3.3 Exploratory Objectives

1) **Objective:** Evaluate antitumor activity using progression-free survival (PFS) by Response Evaluation Criteria in AML or DLBCL (see Section 7.1.2.7.1 and 7.1.2.7.2) as assessed by investigator review, and overall survival (OS).
2) **Objective**: To explore the relationship between genomic variation and response to the treatment(s) administered. Variation across the human genome (germline and tumor) will be analyzed for association with clinical data collected in this study.

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the Investigator's Brochure (IB) for detailed background information on MK-8628.

4.1.1 Pharmaceutical and Therapeutic Background

MK-8628 is a synthetic small molecule targeted to bromodomains (BRD) 2, 3 and 4 of the tandem-BRD-containing family of transcriptional regulators known as the BET (bromodomain extraterminal) proteins.

In cancer, pathologic activation of c-MYC plays a central role in disease pathogenesis, by the coordinated upregulation of a transcriptional program influencing cell division, metastatic adaptation and survival [2][3]. Amplification of MYC is one of the most common genetic alterations observed in cancer genomes [4], and the validation of c-MYC as therapeutic target is supported by numerous lines of experimental evidence [5][6][7][8][9][10]. Nevertheless, despite the central importance of MYC in cancer pathogenesis, conventional approaches toward its direct inhibition have not proven successful. The absence of a clear ligand-binding domain is a formidable obstacle to direct inhibition, a challenging feature shared by many compelling transcriptional targets in cancer [11]. Considering chromatin as a platform for signal transduction [12], the inhibition of MYC transcription and function has been achieved through displacement of chromatin-binding, co-activator proteins, the bromodomains (BRD), using competitive small molecules [13].

BRDs are protein interaction modules that specifically recognize Ɛ-N-acetylated lysine residues [14][15]. BRDs are common in nuclear proteins that regulate gene transcription and chromatin organization and play a key function of recruiting these protein complexes to acetylated chromatin. Dysfunction of BRD-containing proteins has been linked to the development of diverse diseases, and in particular to the development of cancer [16]. BRDs are highly sequence diverse but share a conserved fold comprised of a left-handed bundle of four alpha helices (αZ, αA, αB, αC) [17]. The acetyl-lysine side chain is typically anchored by a hydrogen bond to a conserved asparagine residue and has water-mediated interactions with a conserved tyrosine [15][18]. Crystal structures of BET complexes with di-acetylated histone 4-tail peptides showed that the first BRDs of BRD4 and BRDT may accommodate two acetyl-lysines in a single site [15][19].

The BET family of BRD proteins, which includes BRD2, BRD3, BRD4, and BRD testis-specific protein (BRDT), are epigenetic reader proteins that bind acetylated lysine residues on histones playing critical roles in cellular proliferation and cell-cycle progression [20].

BRD4 binds to the positive transcription elongation factor b (P-TEFb), a cyclin-dependent kinase, and stimulates RNA polymerase II-dependent elongation [21][22]. BRD4 is critical for survival of several diverse tumors due to its function promoting transcription of growth-promoting and anti-apoptotic genes [23], which has prompted the development of potent and selective protein interaction inhibitors targeting BET BRDs.

The biological action of BET proteins occurs through a protein-protein interaction (BET protein binding to an acetylated histone protein) and, as such, this biochemical activity has historically possessed poor tractability for small molecule drug discovery identification. The identification by Chung and colleagues [24] of potent, selective BET inhibitors was not the result an oncology drug discovery effort to "drug" the BRD4 protein to target NMC, but rather was fortuitous, being the result a high-throughput screen to identify molecules for potential use in atherosclerosis (apolipoprotein A1 upregulation). In independent studies during the same time period, Mitsubishi Tanabe scientists reported the discovery and development of thienotriazolodiazepine as a BET inhibitor (including MK-8628) [Mitsubishi Tanabe Pharma Corporation. Antitumor agent. WO 2009084693; 2009]. Building on these findings, Bradner and colleagues synthesized a thienotriazolodiazepine, JQ1[23]. The initial presumption of low tractability of the BET proteins has proven not to be the case, as multiple researchers have identified other potent, selective BET inhibitors with substantially different chemical structures [23][25][26][27]. The crystal structures of these small molecule inhibitors bound to BRD4 illustrate that the binding pocket, which also binds acetyl-lysine, is small, deep, and hydrophobic.

4.1.1.1 Justification of Selecting Subjects with Hematologic Malignancies

Hematologic malignancies are heterogeneous diseases. There is increasing evidence in preclinical models that BRD inhibition can result in antitumor activity against various illnesses, including acute leukemia (AL) [28][29][26][30] to lymphoma [31][32][33] and myeloma [13][34][35]. It is known that in many hematologic malignancies, the oncogenesis is driven by the oncogene c-Myc [13][36][37][38][39]. It has been shown that BRD inhibition was frequently associated with c-Myc, and downstream targets down regulation [38].

Though a significant proportion of subjects with AL and lymphoma can be cured or can benefit of prolonged overall survival with current therapies, the majority of subjects with hematologic malignancies will die from their disease. The level of unmet medical need is therefore very high and innovative new drugs are eagerly expected.

4.1.1.2 MK-8628 Metabolism – CYP Interactions

Results from MK-8628 incubations either with individual recombinant CYPs or with human microsomes and chemical inhibitors to individual CYPs show MK-8628 was metabolized to the mono-hydroxylated metabolite mainly by CYP3A4 and to a lesser extent by CYP2C9 and potentially by CYP2C19, which will need to be confirmed. Results from incubations with individual UDP glucuronosyltransferase(s) (UGT) showed that MK-8628 can be glucuronidated mainly by UGT1A7 and, to a lesser extent, by UGT1A1, 1A10, 1A3, 1A8, and 1A9. MK-8628 inhibits CYP2A6 and 3A4 turnover of probe substrates in microsomes with IC_{50} values that were >10 µM. At 10 µM MK-8628, the inhibition of CYP2A6 and CYP3A4 were 30% and 39%, respectively. MK-8628 has a high apparent permeability (P_{app}

≥21 x 10^{-6} cm/s apical-to-basal) across cell monolayers and is a P-gp substrate. The involvement of several enzymes in the metabolism of MK-8628 reduces concerns for victim drug-drug interaction (DDI). The inhibition of CYP2A6 and particularly CYP3A4 raises concerns that MK-8628 could be a perpetrator in a DDI with co-administered drugs whose clearance is primarily mediated by these enzymes.

4.1.1.3 MK-8628 – Ongoing Clinical Trials in Hematologic Malignancies

Study MK-8628-001 (previously known as OTX015_104), a Phase Ib study in subjects with AL or other hematologic malignancies was started (first subject enrolled) in January 2013. The study is composed of a dose escalation part evaluating MK-8628/OTX015 doses from 10 mg to 160 mg QD in subjects with AL or other hematologic malignancies using a classic 3+3 design, followed by evaluation of dose expansion cohorts in three selected hematologic indications with the QD dosing. The preliminary RD and schedule for the Phase 2 study in hematologic malignancies was 80 mg/day with 14 days on/7 days off schedule, with dose interruptions in the event of grade 4 thrombocytopenia. This preliminary RD will be further explored looking at 20 mg and 30 mg BID continuous dosing. Phase 1 expansion cohorts in AML de novo, AML post-MDS, and DLBCL at 80 mg (14 days on/7 days off) are ongoing. Consideration for further enrollment will be based on findings at additional BID continuous dosing. As of 04-Sep-2015, a total of 135 subjects have been enrolled.

Efficacy data is available for 135 subjects with advanced hematologic malignancies as of 04-Sep-2015. Of 75 subjects with AL, complete responses were observed for 2 subjects (1 subject in the 40 mg QD cohort and 1 subject in the 160 mg QD cohort) and a complete response with incomplete marrow recovery was observed for 1 subject. Of 48 subjects with lymphoma, a complete response was observed for 2 subjects (at 120 mg QD on 14-day and 21- day regimens) and a partial response was observed for 2 subjects (at 80 mg QD on 14-day and 21- day regimens); stable disease was observed for 18 subjects. Of 12 subjects with multiple myeloma, no responses were observed; stable disease was reported for 5 subjects. The duration of response among all responders ranged from 1.4 to 9.2 months.

All 75 subjects with AL had at least 1 AE and 57 (76%) had at least 1 AE considered by the investigator to be drug related. At least 1 AE graded 3 to 5 was observed for 68 (90.7%) subjects and at least 1 drug-related AE was observed for 23 (30.7%) subjects. Drug-limiting toxicity during cycle 1 was reported for 3 (4%) subjects. Serious events were reported for 57 (76%) subjects and serious events that were drug related were reported for 11 (14.7%) subjects. Adverse events led to discontinuation of 22 (29.3%) subjects and AEs considered to be drug related led to discontinuation of 1 (1.3%) subject.

All 60 subjects with other hematologic malignancies (OHM) had at least 1 AE and 49 (81.7%) had at least 1 AE considered by the investigator to be drug related. At least 1 AE graded 3 to 5 was observed for 45 (75%) subjects and at least 1 drug-related AE was observed for 33 (55%) subjects. Drug-limiting toxicity during cycle 1 was reported for 18 (30%) subjects. Serious events were reported for 30 (50%) subjects and serious events that were drug related were reported for 20 (33%) subjects. Adverse events led to discontinuation of 7 (11.7%) subjects and AEs considered to be drug related led to discontinuation of 2 (3%) subjects.

The most common AEs in all subjects pooled (AL and OHM) were hematologic (n=99, 73.3%): anemia (n=60, 44.4%), leukocytosis (n=26, 19.3%), and thrombocytopenia (n=59, 43.7%) (see also Section 7.1); gastrointestinal disorders (n=118, 87.4%): diarrhea (n=88, 65.2%), nausea (n=62, 45.9%), vomiting (n=32, 23.7%), abdominal pain (n=28, 20.7%), and constipation (n=25, 18.5%); general disorders (n=113, 83.7%): asthenia (n=74, 54.8%), pyrexia (n=55, 40.7%), weight decreased (n=30, 22.2%); metabolic (n=83, 61.5%): decreased appetite (n=45, 33.3%), hypokalemia (n=29, 21.5%); musculoskeletal and connective tissue disorders (n=50, 37.0%); nervous system disorders (n=56, 41.5%); psychiatric disorders (n=30, 22.2%); renal (n=29, 21.5%); respiratory: cough (n=37, 27.4%), dyspnea (n=36, 26.7%), and epistaxis (n=29, 21.5%); skin and subcutaneous tissue disorders (n=60, 44.4%); and vascular disorders (n=30, 22.2%).

Notable were investigations: hyperbilirubinaemia (n=10, 7.4%). It's plausible that the mechanism to explain clinical hyperbilirubinemia could be the competitive inhibition of enzymes and transporters involved in the disposition of bilirubin and its conjugates. The competitive inhibition could be mediated by parent MK-8628 and/or its metabolites. Experiments are ongoing to attempt to elucidate this mechanism.

Additional details can be found in the Investigator's Brochure (IB).

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

In the present study, adult subjects with selected hematologic malignancies with the potential to respond to BET inhibition (AML De Novo and Post MDS, and DLBCL) will receive MK-8628/OTX015 orally to determine the RD for phase II studies. QD evaluations were previously evaluated in study MK-8628-P001/OTX015_104. This study will focus on the evaluation of a BID regimen.

MK-8628, a pan-BET bromodomain inhibitor, shows activity in several preclinical hematologic and somatic cancer models. Meaningful antitumor activity has also been reported in subjects with heavily pretreated hematological malignancies in the ongoing phase I clinical study treated with MK-8628. Accumulating studies reveal the critical roles of BET bromodomains in cancer development.

Several experimental cancer models have demonstrated the functional consequences of BET protein overexpression and translocation:

- B-cell restricted constitutive expression of BRD2 in mice inappropriately transactivates the cyclin A gene in pre-malignant B cells [31] to cause a malignancy that is highly similar to DLBCL [32]. The BRD2-driven DLBCL in mice can be cured with the standard regimen of cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP) chemotherapy used to treat human DLBCL [33].
- The MLL (mixed lineage leukemia) gene is one of the most frequently involved genes in both lymphoblastic and myeloid leukemias. A global proteomic strategy found that MLL fusions, as part of super elongation complex (SEC) and the polymerase-associated factor complex (PAFc), are associated with the BET family of proteins [26]. Treatment with

BET inhibitors was shown to provide a survival advantage in three MLL leukemia models [26][29].

Taken together, preclinical data and results from the ongoing phase Ib hematologic study (MK-8628-001) provide the rationale for further investigating MK-8628 in subjects with selected hematologic malignancies.

4.2.2 Rationale for Dose Selection/Regimen/Modification

In the previous hematologic phase I study (OTX015_104 / MK-8628-001), a dose escalation was completed and preliminary results of the cohort expansion are available. As of June 2015, a total of 87 subjects had been included in the dose escalation part in the two cohorts (AL and OHM), and a further 49 subjects had been included in three dose expansion cohorts. A QD schedule was evaluated at all levels (up to 160 mg) and a 40 mg BID schedule was also evaluated.

The preliminary RD for the QD schedule was 80 mg QD, with a 14 days ON/7 days OFF schedule for both the OHM and the AL cohorts. DLT of thrombocytopenia was the prevalently observed AE in the OHM cohort, occurring above 40 mg QD. At DL4, thrombocytopenia was more frequent at 40 mg BID with a higher incidence of thrombocytopenia compared to the equivalent total dose per day given as QD, i.e., 5/6 subjects vs. 2/7 subjects, respectively - making the dose of 40 mg BID unacceptable with >33% of DLT in this cohort. The main limiting toxicities reported are thrombocytopenia, fatigue, gastrointestinal toxicities, as well as asymptomatic bilirubin increases and Factor VII decreases.

Preliminary clinical activity has been observed at a range of dose levels, including objective responses at 40 mg QD (1 CR), 80 mg (CRi) and 160 mg (CR) in the AL cohort and at 80 mg QD (1 PR) and 120 mg (2 CR) in DLBCL subjects.

A total of 49 subjects had been treated in the expansion cohorts with non-continuous dosing at 80 mg QD, 14 days ON/7 days OFF: 16 AML post-MDS subjects, 18 AML non-MDS related (i.e. de novo, secondary to chemotherapy or MPD) subjects, and 15 DLBCL subjects. The expansion cohort demonstrated that at 80 mg QD, 14 days ON/7 days OFF was reasonably well tolerated with no DLTs reported. However, one subject with AML had grade 3 asthenia, deemed not related by the investigator after clarification (related to aspergillosis), and one subject with AML had a dose reduction due to poor tolerance (asthenia, anorexia, dysgeusia G2).

In the dose expansion cohort, one PR has been reported to date in a DLBCL subject along with evidence of clinical activity not yet meeting standard response criteria in some ongoing subjects (decrease in bone marrow blasts in five AML subjects and decreased lymph node lesions in two DLBCL subjects).

4.2.2.1 Starting Dose for This Trial

Data is now emerging on how to better dose epigenetic therapies, including more frequent dosing that avoids undesirable effects mediated by higher concentrations and resultant enhanced broad inhibition of the targeted genes. The limited number objective responses in

the dose expansion cohorts in the hematologic malignancies study where MK-8628 was given in a discontinuous manner (i.e. 14 days ON/7 days OFF) raises the question of whether there is a need for continuous and sustained target inhibition. On the basis of several translational and clinical studies, low, prolonged drug exposure is becoming the hallmark of successful epigenetic modulation [40]. Notable epigenetic agents where this phenomenon is observed include FDA-approved DNMT inhibitors such as 5-azacitidine and decitabine [41]. Clinical development of these agents was initially hindered because early trials used higher, infrequent doses that proved to be substantially toxic to subjects (likely because of off-target epigenetic modulation). Lower, continuous dosing was found to markedly decrease treatment-related AEs and enhance targeted effects on DNA methyltransferases because the concentrations are maintained at a level where cytotoxic effects are not the prevailing mode of action. The available data support the notion that maintaining concentrations that avoid immediate cytotoxic effects but engage the target in a continuous fashion allows for reprogramming of the tumor cells that can alter disease biology in a durable, clinically meaningful manner [40].

Therefore, to maintain or sustain target inhibition with MK-8628 and mitigate daily fluctuations in systemic concentrations, a more frequent dosing schedule will be evaluated in this protocol using BID dosing. The hypothesis underlying this approach is that a higher Ctrough achieved with lower, more frequent dosing may be needed to disrupt super-enhancer driven oncogene expression (e.g., Myc, Bcl-2) over longer periods of time in order to induce antitumor activity [38]. Enhanced preclinical efficacy seen with the BET inhibitor JQ1 and MK-8628 with more frequent dosing (BID versus QD) seen in preclinical evaluations [26][38][42] is likely attributable to the ability of these powerful gene expression enhancers to quickly restore oncogene expression once the compound exposure wanes. Considering the short half-life for MK-8628 of ~5-6 hours, BID dosing has the potential to maintain sustained target engagement at a lower dose (i.e. lower Cmax could help avoid off-target toxicities).

Based on available PK data and results suggesting MK-8628 exhibits dose proportional exposure and a half-life much shorter than either a 12-hour or 24-hour dosing interval, a Ctrough 12 hours after BID dosing will more than likely result in significantly higher concentrations than a Ctrough of double the same dose at 24 hours (~4 cumulative half-lives). For example, the MK-8628 PK results from both cohorts combined shown in Figure 1 demonstrate that a 40 mg BID dose attains significantly higher Ctrough than a similar daily dose of 80 mg QD. In the absence of a clear understanding of target engagement at different doses and an appropriate efficacious dose, total daily doses up to 60 mg administered as BID (i.e., max of 30 mg BID) or additional dose schedules will be evaluated with the hypothesis that more frequent dosing may improve efficacy.

Because epigenetic reprogramming can take longer to become apparent than the actions of traditional chemotherapies, a continuous prolonged course of treatment may be required for efficacy evaluation. Balancing this against risk (thrombocytopenia) and tolerability issues (as seen in the initial dose escalation), a lower, more frequent BID dosing schedule will be explored primarily for Proof of Concept (POC).

In Figure 2 below, PK comparison of QD versus BID in the combined dose escalation cohorts suggests that C_{trough} or time above threshold could underlie hematologic toxicity and potentially efficacy of MK-8628. PK data suggest no difference in total exposure (top graph).

Median daily AUC of 40 mg BID is similar to 80 mg QD. However, there is a large difference in median trough concentration (bottom graph).

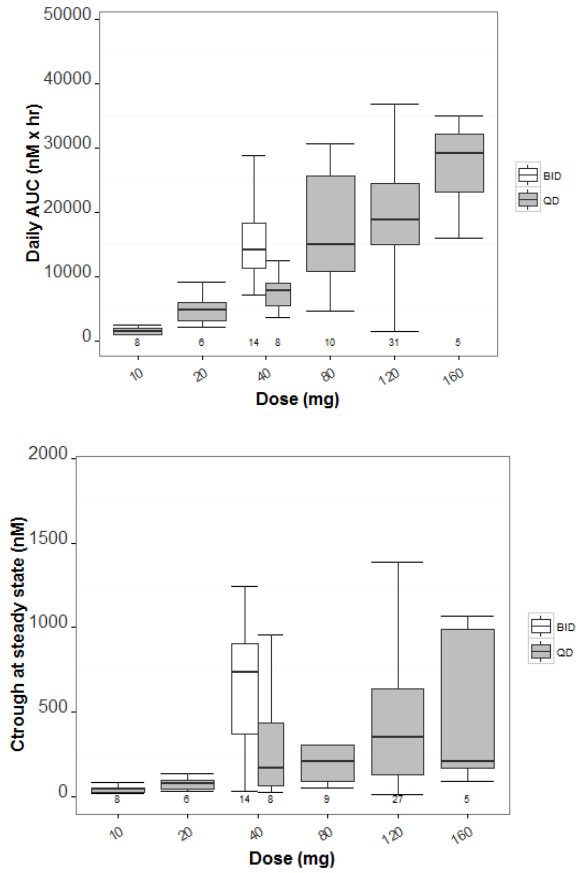


Figure 2 PK comparison of QD versus BID

4.2.2.2 Maximum Dose/Exposure for This Trial

The maximum dose for the BID regimen in this study will be the highest dose level tolerated (< 25% DLT rate).

4.2.2.3 Rationale for Dose Interval and Trial Design

The purpose of this trial is to determine the recommended phase 2 dose (RP2D) of MK-8628 for further phase II trials in subjects with selected hematologic malignancies that might benefit from BET inhibition. The RP2D of BID administration regimens will be explored using a 6+8 two-stage design which offers a fast approach with continuous DLT rate monitoring via a modified toxicity probability index (mTPI)(Ji design)[1].

4.2.3 Rationale for Endpoints

4.2.3.1 Safety Endpoints

4.2.3.1.1 Primary Safety Endpoint:

A primary objective of this trial is to determine the recommended phase II dose (RP2D) of MK-8628. Selecting the RP2D will involve a multi-faceted decision taking into account safety, tolerability, early efficacy signal, PK exposure and PD markers. The primary endpo int driving dose selection is the DLT rate, with weight given to the highest DL tolerated (< 25% DLT rate). All other facets will be considered supportive. It is important to note that dose selection in this study aims to assess a recommended phase 2 dose *range*, with other factors aside from those mentioned above, such as target engagement, contributing to refining the dose selection for phase 2. This will be further evaluated in subsequent clinical investigations in either monotherapy or combination trials**.**

Secondary Safety Endpoints

The secondary safety endpoint will be to evaluate the safety and tolerability of MK-8628 across subjects with AML (de Novo and post-MDS) and DLBCL included in this trial. Safety will be assessed in subjects who have received MK-8628 by determining the RP2D and quantifying and grading reported AEs using CTCAE, Version 4.0. Attribution to drug, time-of-onset, duration of the event, resolution, and any concomitant medications administered will be recorded. AEs to be analyzed include but are not limited to all AEs, ECIs, SAEs, fatal SAEs, and laboratory changes.

4.2.3.2 Pharmacokinetic Endpoints

Plasma parameters of MK-8628 as appropriate and according to analyses performed (non-compartmental or nonlinear mixed effect modelling) will be determined and may include trough (Cmin) and peak (Cmax) concentrations, Tmax, AUC[0-∞], Vdss, t1/2, steady state, total clearance (CL). PK data for MK-8628 will be interpreted in terms of safety findings and compared with historical data. Incidence and severity of AEs along with PK parameters will be analyzed in relation to the most pertinent biomarker(s), if any.

Pharmacodynamic Endpoints

Inhibition of BET proteins by MK-8628 leads to alterations in the transcription of mRNA at loci most sensitive to disruption of BET activity. These are considered target genes. Changes in expression, measured via mRNA, of prespecified target genes* will be used as PD biomarkers to assess target engagement of BET proteins by MK-8628. (*Note: the following non-exhaustive list of target genes may be considered for testing: Bcl2, IL7R, and MYC as down-regulated target genes; CSRNP2, HEXIM1, and HIST1H2BK as up-regulated target genes.) A range of PD biomarkers will be explored in surrogate samples from all subjects treated, using appropriate assays to establish target engagement. Rather than rely on gene expression changes in cancer cells, these PD biomarkers will be based on current PD knowledge from translational studies of mouse and human whole blood (e.g. Figure 3 below). Using RNA extracted from whole blood samples collected both prior to and following administration of MK-8628, messenger RNA transcript profiling may be performed to assess gene expression and evaluate whether changes in specific genes or sets

of genes may represent a PD biomarker of response. Potential limitations of this assay include subject-to-subject variability and a small effect size of induction or repression upon treatment with MK-8628. Due to these limitations, the PD endpoint is considered to be qualitative given the assay may not be able to differentiate target engagement between the MK-8628 doses examined in this study.

See Figure 3. Whole blood from 6 normal healthy volunteers was treated with either vehicle (0.1% DMSO) or increasing concentrations of MK-8628. After 4 hours, whole blood was lysed (PAXgene tube) and mRNA extracted for qPCR analysis of candidate BET target genes. Data were normalized (ΔCt) by PPIB and plotted for all six individuals as change in ΔCt.

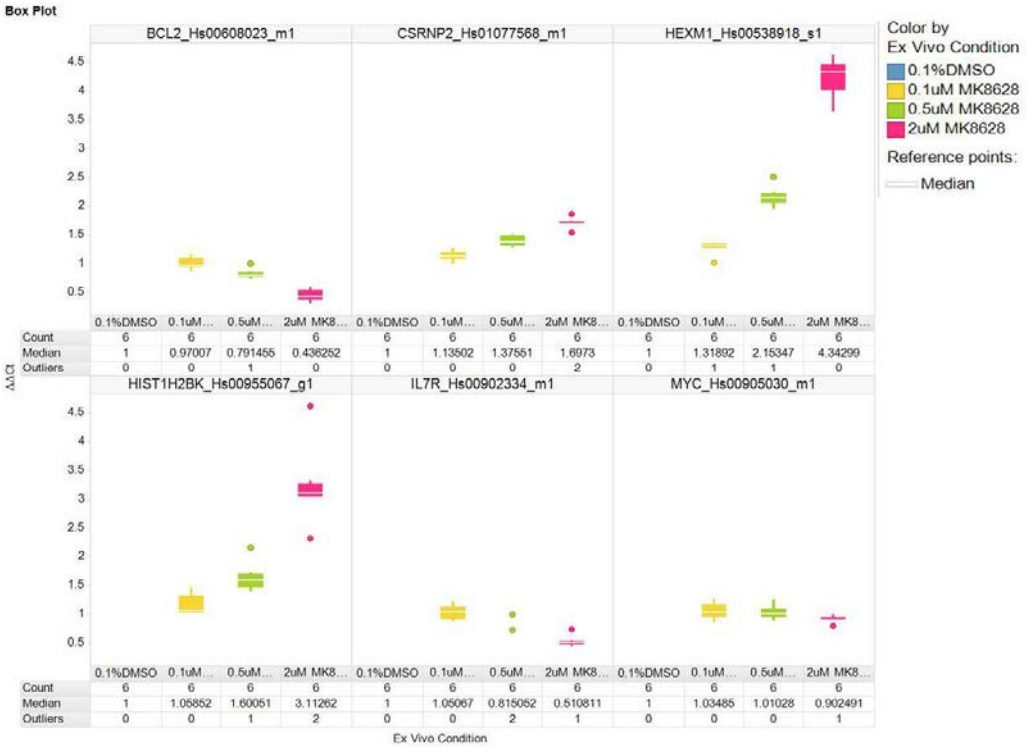


Figure 3 Dose-Dependent Changes in BET Protein Target Gene Expression in Human Whole Blood Ex Vivo

4.2.3.3 Efficacy Endpoints

4.2.3.3.1 Secondary Efficacy Endpoints

The secondary efficacy objectives for this trial are to evaluate the anti-tumor activity of MK-8628 in subjects with AML (de Novo and post-MDS) and DLBCL biomarker unselected. Secondary efficacy endpoints include (1) ORR, defined per standard response criteria for acute leukemia (Section 12.4) and malignant lymphoma (Sections 12.5), as assessed by investigator, (2) DOR, defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first, (3) disease control rate defined as the percentage of subjects with advanced or metastatic cancer who have achieved CR, PR and stable disease.

4.2.3.3.2 Exploratory Efficacy Endpoints

Exploratory efficacy endpoints include PFS, defined as the time from allocation to the first documented disease progression according to Response Evaluation Criteria in AML or DLBCL (see Section 7.1.2.7.1 and 7.1.2.7.2), or death due to any cause, whichever occurs first, and OS.

4.2.3.4 Planned Exploratory Biomarker Research

Planned Genetic Analysis

Understanding genetic determinants of drug response is an important endeavor during medical research. This research will evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or adverse events, the data might inform optimal use of therapies in the patient population. This research contributes to understanding genetic determinants of efficacy and safety associated with the treatments in this study.

4.2.3.5 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on specimens collected for future biomedical research during this clinical trial. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma) and/or the measurement of other analytes.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that subjects receive the correct dose of the correct drug/vaccine at the correct time. The details of this Future Biomedical Research sub-trial are presented in Section 12.2 - Collection and Management of Specimens for Future Biomedical Research. Additional informational material for institutional review boards/ethics committees (IRBs/ERCs) and investigational site staff is provided in Section 12.3.

4.3 Benefit/Risk

Subjects in clinical trials generally cannot expect to receive direct benefit from treatment/vaccination during participation, as clinical trials are designed to provide information about the safety and effectiveness of an investigational medicine.

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying Investigators Brochure (IB) and Informed Consent documents.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male and female subjects with either AML (de Novo and post-MDS) or DLBCL ≥18 years of age will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Be willing and able to provide written informed consent for the trial. Study entry is defined as the date that subject provides written informed consent. The subject may also provide consent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical research.
2. Be ≥ 18 years of age on the day of providing written informed consent.
3. Have an ECOG performance status score of ≤ 1.
4. Have an interval of ≥ 3 weeks since chemotherapy (≥ 6 weeks for nitrosoureas or mitomycin C), immunotherapy, hormone therapy or any other anticancer therapy (including investigational) or surgical intervention resection, or ≥ 3 half-lives for monoclonal antibodies, or ≥ 5 half-lives for other non-cytotoxic agents (whichever is longer).
5. Female subjects of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
6. Female subjects of childbearing potential should be willing to use an adequate method of contraception as outlined in section 5.7.3 - Contraception, for the course of the study through 90 days after the last dose of study medication. Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.
7. Male subjects of childbearing potential 5.7.3 – Contraception, starting with the first dose of trial treatment through 90 days after the last dose of study medication. Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject
8. Demonstrate adequate organ function as defined in Table 1 below. All screening labs should be performed within 7 days of treatment initiation.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	AML Subjects = No Limit DLBCL Subjects = ≥ 1.0 x 10^9/L
Platelets	AML Subjects = No Limit DLBCL Subjects = ≥ 150 x 10^9/L (4 weeks without transfusion)
Hemoglobin	AML Subjects = No Limit DLBCL Subjects = ≥ 8.0 g/dL (4 weeks without transfusion)
Renal	
Creatinine clearance	≥ 30 mL/min calculated according to the Cockroft and Gault formula or MDRD formula for subjects aged ≥ 65 years (see Section 12.7)
Hepatic	
Serum total bilirubin	≤ 1.25 X ULN **OR** In case of liver involvement, ≤ 2 X ULN will be allowed
AST (SGOT) and ALT (SGPT)	≤ 3 X ULN
Alkaline Phosphatase	If > 2.5 X ULN, then liver fraction should be ≤ 2.5 X ULN
Chemistry	
Serum albumin	≥ 2.8 g/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤ 1.5 X ULN
Activated Partial Thromboplastin Time (aPTT)	≤ 1.5 X ULN

9. Have a histologically or cytologically proven malignancy (AML or DLBCL) according to the WHO 2008 classifications [43][44]. AML includes AML de novo and AML secondary to a pre-existing myelodysplastic syndrome.

   The subject must also display the following specific malignancy criteria:

   a) AML (de Novo and post-MDS):

   - Subjects must have measurable and evaluable disease per tumor response criteria (see Section 7.1.2.7.1).
   - Subjects must have ≥ 5% bone marrow blasts at study entry, without alternative causality (e.g. bone marrow regeneration).
   - Subjects < 60 years old in second or further relapse or relapsing after allogeneic stem cell transplantation regardless of number of relapses.

- Subjects ≥ 60 years old in first relapse* with a disease-free interval (DFI) < 12 months, or further relapse. If locally approved therapies exclude patients in this age group, with no prior lines of therapy, these patients will be considered eligible per local requirements.

  *Note: First relapse is also applicable to AML post-MDS patients who have received prior treatment for MDS, but have not received prior treatment for AML.

- Irrespective of age, in subjects relapsing after allogeneic stem cell transplant, the time elapsed since allogeneic stem cell transplant should be > 90 days.
- Subjects with Philadelphia chromosome positive (Ph+) must have received at least two lines of therapy, including 2 bcr-abl tyrosine-kinase (TK) inhibitors (among imatinib, nilotinib and dasatinib), or only one line including one TK inhibitor if the relapse/refractoriness is associated with the detection of a resistance mutation to these inhibitors.

b) DLBCL:

- Subjects must have measurable and evaluable disease per tumor response criteria (see Section 7.1.2.7.2).
- Subjects must have at least one non-irradiated tumor mass ≥ 15 mm (long axis of lymph node) or ≥ 10 mm (short axis of lymph node or extranodal lesions) on a spiral CT-scan.
- Subjects having failed 2 standard lines of therapy (at least one containing an anti-CD20 monoclonal antibody), or for whom such treatment is contraindicated.

5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Has participated in another clinical trial or treatment with any investigational drug (excluding anticancer treatments) within 30 days prior to study entry.
2. Has other concomitant anticancer treatment.
3. Has persistent grade >1 clinically significant toxicities related to prior antineoplastic therapies (except for alopecia); stable sensory neuropathy ≤ grade 2 NCI-CTCAE v. 4.0 is accepted.
4. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.
5. Has taken a similar class of therapy previously (BET inhibitor).
6. Has inability to swallow oral medications or presence of a gastrointestinal disorder (e.g. malabsorption) deemed to jeopardize intestinal absorption of MK-8628.

7. Has known primary CNS malignancy or symptomatic or untreated CNS metastases.
8. Has other serious illness or medical condition, such as active infection, unresolved bowel obstruction, psychiatric disorders, or cerebrovascular accident (within 1 year of study entry).
9. Has known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies). HIV 1/2 antibodies testing is only required when the investigator has reason to suspect the patient has Human Immunodeficiency Virus infection.
10. Has known active Hepatitis B (e.g. HBsAg reactive) or Hepatitis C (e.g. HCV RNA [qualitative] is detected). Hepatitis B surface Antigen reactive testing and HCV RNA [qualitative] testing is only required when the investigator has reason to suspect the patient has Hepatitis B infection or Hepatitis C infection.
11. Has received high dose chemotherapy followed by autologous stem cell transplantation less than 90 days prior to first dose of MK-8628.
12. Has concomitant (and cannot discontinue) therapy with strong CYP3A4 or CYP2A6 interfering drugs, or any other medication / therapy prohibited by the protocol. Please see Section 5.5 .
13. Has peripheral cytopenia (i.e. auto-immune hemolytic anemia or thrombocytopenia).
14. Has acute promyelocytic leukemia or clinically uncontrolled (i.e. with bleeding) disseminated intravascular coagulation (DIC).
15. Has chronic graft versus host disease (GVHD) or on immunosuppressive therapy for the control of GVHD.
16. Has uncontrolled disease-related metabolic disorder (e.g. hypercalcemia).
17. Is pregnant or breast-feeding.
18. Has any of the following cardiac related conditions:
    a) Congestive heart failure (except if medically controlled)
    b) Angina pectoris (except if medically controlled)
    c) Previous history of myocardial infarction (within 1 year of study entry)
    d) Uncontrolled hypertension (defined as systolic blood pressure (SBP) ≥ 140 mm Hg and/or diastolic blood pressure (DBP) > 90 mm Hg and not adequately managed by anti-hypertensive medication)
    e) Uncontrolled arrhythmias

5.2 Trial Treatment(s)

The treatment to be used in this trial is outlined below in

Table 2 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
MK-8628	20 mg	BID	Oral	Continuous / 21 days per cycle	Experimental
MK-8628	30 mg	BID	Oral	Continuous / 21 days per cycle	Experimental

The first dose of trial treatment will be administered at the trial site in the morning of the Cycle 1 Day 1 Visit, and then again in the evening. Subsequent dosing will be performed twice daily either at the trial site on scheduled visit days, or by the subject (i.e., unsupervised at his/her home), at approximately the same times each day.

All supplies indicated in Table 2 above will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

For any commercially available product that is provided by the trial site, subsidiary or designee every attempt will be made to source these supplies from a single lot/batch number. The trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of trial treatments in accordance with the protocol and any applicable laws and regulations.

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection (Preparation)

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background & Rationale. There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each subject.

5.2.1.2 Dose Escalation

A twice daily (BID) dose escalation will be performed using a 6+8 two-stage design with continuous DLT rate monitoring via a modified toxicity probability index (mTPI) (Ji design), targeting a maximum 25% DLT rate [1].

Two planned dose levels will be evaluated sequentially: 20 mg BID and 30 mg BID (all continuous daily). See Table 3 and Table 4 for the dose escalation scheme.

Table 3 Dose Escalation Scheme

Dose Level (DL)	MK-8628 (mg/dose) BID Regimen (continuous)	Outcome (#DLT/#Subjects)* / Actions to be taken
DL 1	20	**At each DL**: - Escalate/de-escalate per DLT rate observed using mTPI (Table 4)
DL 2	30	

* Evaluated during the first 21 days of treatment

Table 4 Modified Toxicity Probability Interval (mTPI) Design

	Number of subjects treated at current dose								
Number of toxicities	6	7	8	9	10	11	12	13	14
0	E	E	E	E	E	E	E	E	E
1	S	E	E	E	E	E	E	E	E
2	S	S	S	S	S	S	S	S	E
3	D	S	S	S	S	S	S	S	S
4	DU	DU	DU	D	S	S	S	S	S
5	DU	DU	DU	DU	DU	D	S	S	S
6	DU	DU	DU	DU	DU	DU	DU	DU	D
7		DU	DU	DU	DU	DU	DU	DU	DU
8			DU	DU	DU	DU	DU	DU	DU
9				DU	DU	DU	DU	DU	DU
10					DU	DU	DU	DU	DU
11						DU	DU	DU	DU
12							DU	DU	DU
13								DU	DU
14									DU

E = Escalate to the next higher dose
S = Stay at the current dose
D = De-escalate to the next lower dose
DU = The current dose is unacceptably toxic
Target toxicity rate = 25%

E = Escalate; S = Stay; D = De-escalate; DU = Unacceptable

Note:

- De-escalation at lowest dose level indicates stopping of trial
- Escalation at highest dose level indicates staying at that level

Each cohort (AML and DLBCL) will be evaluated independently in regards to enrollment and dose level escalation/de-escalation.

Subjects may be enrolled continuously (i.e., without waiting for Cycle 1 completion of subjects who have received the first dose) unless a DLT is observed at the particular dose. If 0 out of the first 6 subjects in a given dose level develop a DLT, then the dose can escalate to the next level without further expansion. If 3 patients out of the first 6 patients develop a DLT, the dose will be de-escalated to the next lowest dose level. If ≥ 4 out of the first 6 patients develop a DLT, this indicates an unacceptable toxicity. If 1 to 2 out of the first 6 subjects of a given dose level develop a DLT, expand the current dose level according to Table 4 by continuing enrollment as follows. The number of subjects who are enrolled at that dose but are not yet fully evaluable for DLT assessment may not exceed the number of remaining subjects who are at risk of developing a DLT before the dose would be considered unacceptably toxic (denoted as DU in Table 4). For example, if 2/7 subjects have experienced a DLT at a given dose level, no more than an additional 3 subjects should be enrolled at this dose level until additional DLT data are available. This is because this dose level would be considered unacceptably toxic if all 3 of the additional subjects experience a DLT (i.e., 5/10 subjects with DLT in Table 4). To find out how many more subjects can be enrolled, one can count steps in diagonal direction (down and to the right) from the cell (7 subjects, 2 toxicities) to the first cell marked DU.

De-escalation (D) or unacceptable (DU) at the lowest dose level (DL1) indicates stopping of the trial. Escalation (E) at the highest dose level (DL2) indicates staying at that level. Note that while 25% has been the target toxicity rate used to generate the guidelines in Table 4, the observed rate of subjects with DLT at the RP2D may be slightly above or below 25%.

Subjects not evaluable for DLT (i.e. receiving less than 85% of the intended cumulative dose in Cycle 1 for any reason other than toxicity; < 18 days of treatment) and who do not experience DLT will be replaced.

Subjects will receive MK-8628 at the DL they were assigned at treatment allocation throughout the study, or at a reduced dose according to toxicity encountered.

A Safety Review Committee will meet on a regular basis to make decisions related to current dose level duration, escalation, de-escalation, and stopping of the trial. Decisions will be based on available safety and toxicity data. The Safety Review Committee will be composed of an independent medical expert in oncology drug development, the principal investigators (or sub-investigator delegated by the PI) from each of the participating sites, the PK investigator, and Sponsor representatives.

5.2.1.3 Definition of Dose Limiting Toxicity

DLT is defined as any of the following toxicities occurring during the first cycle of treatment (21 days) for each dose level. See Section 5.9 for rules on replacement of subjects in the DLT period.

The occurrence of any of the following toxicities during Cycle 1, **if assessed by the investigator to be possibly, probably or definitely related to MK-8628**, will be considered a DLT**:**

Hematologic Toxicity:

AML

1. Pancytopenia with a hypocellular bone marrow and no marrow blasts lasting for ≥ 6 weeks after the start of a cycle. For subjects with AML who have a suspected DLT in case of pancytopenia with a hypocellular bone marrow and no marrow blast on Day 22 bone marrow aspiration, the DLT window will be extended to the first 2 cycles or Day 42 for repeat bone marrow confirmation. However, enrollment of additional patients at this dose level should not be delayed during the extended window for DLT in this situation assuming a confirmed DLT for such a subject would not affect a dose escalation or de-escalation decision.

DLBCL

1. Grade 4 hematologic toxicity lasting ≥ 7 days, except thrombocytopenia

   Grade 4 thrombocytopenia of any duration

   Grade 3 thrombocytopenia is a DLT if associated with bleeding
2. Febrile or infection related neutropenia, Grade 3 or Grade 4

Non-Hematologic Toxicity:

1. Grade 4 non-hematologic toxicity (not laboratory)
2. Grade 3 non-hematologic toxicity (not laboratory) lasting > 3 days despite optimal supportive care. Grade 3 nausea, vomiting or diarrhea will be considered a DLT if lasting more than 3 days despite optimal supportive care.
3. Any Grade 3 or Grade 4 non-hematologic laboratory abnormality, if
   - medical intervention is required, or
   - the abnormality leads to hospitalization, or
   - the abnormality persists for > 1 week
4. Any of the following liver test abnormalities** are observed (see also Section 12.8):
   - ALT or AST > 8X ULN
   - ALT or AST > 5X ULN for more than 2 weeks
   - ALT or AST > 3X ULN **AND** (total bilirubin > 2X ULN **OR** INR > 1.5)
   - ALT or AST > 3X ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%), unless the investigator assesses the rash or fatigue to be related to MK-8628 and not related to liver impairment with sponsor's agreement.

Other Toxicity:

1. Any drug-related AE which caused subject to discontinue treatment during Cycle 1
2. Any study drug-related toxicity resulting in a subject missing ≥ 20% of planned doses during Cycle 1.
3. Any treatment-related toxicity which causes a greater than 2 week delay in initiation of Cycle 2.
4. Grade 5 toxicity

DLTs must be reported within 24 hours to the Sponsor as Events of Clinical Interest (see Section 7.2.3.2). If the event also meets the criteria for seriousness, follow the reporting guidelines for Serious Adverse Events (SAEs) outlined in Section 7.2.3.1.

5.2.1.4 Recommended Phase 2 Dose (RP2D)

Selecting the RP2D will involve a multi-faceted decision taking into account safety, tolerability, early efficacy signal, PK exposure and PD markers. The primary endpoint driving dose selection is the DLT rate, with weight given to the highest DL tolerated (< 25% DLT rate). All other facets will be considered supportive. It is important to note that dose selection in this study aims to assess a recommended phase 2 dose range, with other factors aside from those mentioned above, such as target engagement, contributing to refining the dose selection for phase 2. This will be further evaluated in subsequent clinical investigations in either monotherapy or combination trials.

5.2.1.5 Dose Adaptation

The Common Terminology Criteria for Adverse Events version 4.0 (CTCAE 4.0) must be used to grade the severity of adverse events. For AEs not specifically addressed in Section 5.6, MK-8628 will be withheld for drug related Grade 4 hematologic toxicities, non-hematological toxicity ≥ Grade 3 including laboratory abnormalities, and severe or life-threatening AEs as per Table 5 below. If a dose of MK-8628 is withheld for toxicity, then subjects may resume dosing with MK-8628 if that is appropriate at their next scheduled appointment or when toxicity has improved as described below or in Section 5.6.

Table 5 Dose Modification Guidelines for Drug-Related Adverse Events

Toxicity	Grade	Hold Treatment (Y/N)	Timing for restarting treatment	Dose/Schedule for restarting treatment	Criteria for discontinuation after consultation with Sponsor
Hematologic toxicity **DLBCL**	1, 2, 3	No	N/A	N/A	N/A
	3 associated neutropenia with infection; or Thrombocytopenia with bleeding or lasting > 7 days	Yes	Toxicity resolves to Grade 0-1, or to baseline	Resume treatment at next lowest dose level (Table 6)	Toxicity does not resolve within 2 weeks of last dose. *Permanent discontinuation should be considered for any severe or life-threatening event*
	4 or Febrile neutropenia	Yes	Toxicity resolves to Grade 0-1, or to baseline	Resume treatment at next lowest dose level (Table 6)	Toxicity does not resolve within 2 weeks of last dose. *Permanent discontinuation should be considered for any severe or life-threatening event*
Hematologic toxicity **AML**	1, 2, 3	No	N/A	N/A	N/A
	4 or Pancytopenia with a hypocellular bone marrow and no marrow blasts lasting ≥ 6 weeks after the start of a cycle.	Yes	Toxicity resolves to Grade 0-1, or to baseline	Resume treatment at next lowest dose level (Table 6)	Toxicity does not resolve within 2 weeks of last dose. *Permanent discontinuation should be considered for any severe or life-threatening event*

Toxicity	Grade	Hold Treatment (Y/N)	Timing for restarting treatment	Dose/Schedule for restarting treatment	Criteria for discontinuation after consultation with Sponsor
Non-Hematologic Laboratory Abnormalities	1, 2	No	N/A	N/A	N/A
	3, 4 with or without symptoms lasting > 48 hours	Consider holding; Hold treatment for total bilirubin increases >2X ULN or 2X baseline (if elevated at baseline) and/or AST or ALT ≥ 5X ULN	Toxicity resolves to Grade 0-1, or to baseline	Laboratory abnormalities resolves within 1 week: treat at same dose and schedule Laboratory abnormalities does not resolve within 1 week: may consider resuming treatment at next lowest dose level (Table 6)	Toxicity does not resolve within 2 weeks of last dose. *Permanent discontinuation should be considered for any severe or life-threatening event*
Non-Hematologic toxicity Note: Exception to be treated similar to Grade 1 toxicity • Grade 2 alopecia • Grade 2 fatigue	1	No	N/A	N/A	N/A
	2 Any intolerable G2 non-hematologic toxicity lasting >7 days with or without dose reduction	Consider holding for persistent symptoms	Toxicity resolves to Grade 0-1 or baseline	Clinical AE resolves within 2 weeks: treat at same dose and schedule Clinical AE does not resolve within 2 weeks: may consider resuming treatment at next lowest dose level (Table 6)	Dose is interrupted for > 2 weeks.
	3, 4 unless not optimally treated with supportive care (e.g., Grade 3 vomiting not adequately treated according to anti-emetic standard of care)	Yes	Toxicity resolves to Grade 0-1 or baseline	Resume treatment at next lowest dose level (Table 6)	Toxicity does not resolve within 2 weeks of last dose. *Permanent discontinuation should be considered for any severe or life-threatening event*

After recovery from toxicity, treatment will be resumed at the next lowest dose level (Table 6). For subjects treated at DL1 (20 mg BID), treatment will be resumed at a level of 10 mg BID.

Table 6 MK-8628 Dose and Schedule Modifications

Dose Level (DL)	Initial Dose	1st Modification
DL 1	20 mg BID continuous	10 mg BID continuous
DL 2	30 mg BID continuous	20 mg BID continuous

No more than one dose reduction should be implemented unless the investigator thinks it in the subject's best interests to pursue study treatment with further dose reduction (additional dose reduction by one dose level), with the Sponsor's agreement.

Dosing interruption for > 2 weeks due to toxicity will lead to definitive study treatment discontinuation, unless the investigator thinks it in the subject's best interests to pursue study treatment, with the Sponsor's agreement.

5.2.2 Timing of Dose Administration

MK-8628 is to be administered orally with water in a fasted state, and as part of a BID regimen (twice daily, approximately 12 hours apart). Subjects should not have food for 1 hour before or 3 hours after study drug administration.

Dosing not performed at the same time (±2h) as on other days should be skipped. Subjects are to be instructed that if they vomit or omit their dose in that time frame, it is not to be replaced. Capsules must not be opened or chewed.

A treatment cycle is 21 days (3 weeks). The subsequent cycle will begin on day 22 or after recovery from any AEs to baseline or Grade < 2 associated with the previous cycle.

Subjects should receive study treatment within 3 days following treatment allocation.

Details of the exact dose and time of administration will be documented in a validated subject diary and reported in the electronic case report form (eCRF).

5.2.2.1 Premedication

No systematic premedication will be given at least during the first cycle. See section 5.5 for a list of allowed and prohibited medications.

5.2.3 Trial Blinding

This is an open-label trial; therefore, the Sponsor, investigator and subject will know the treatment administered.

5.3 Randomization or Treatment Allocation

Cohort management and treatment allocation will occur centrally using an interactive web response system (IWRS). Subjects will be allocated to treatment by non-random assignment based on the open dosing cohort and number of available slots.

5.4 Stratification

No stratification based on age, sex or other characteristics will be used in this trial.

5.5 Concomitant Medications/Vaccinations (Allowed and Prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the investigator, the Sponsor and the subject.

5.5.1 Medications

All treatments taken by subjects at study entry or within 4 weeks or 5 half-lives prior to initiating treatment (whichever is longer) or at any time during the study, in addition to the investigational product are considered concomitant medications and must be documented in the eCRF.

No premedication is planned.

Allowed

Listed below are allowed concomitant medications / therapy during the course of the trial:

1. Supportive treatment of symptoms/adverse events or standard treatment of concomitant conditions, notably transfusion support and antibiotics or bisphosphonates will be given as medically indicated and reported in the eCRF.
2. Chemotherapy, hormone therapy or any other anticancer therapy or surgical intervention resection performed ≥ 3 weeks prior to study start (≥ 6 weeks for nitrosoureas or mitomycin C) or ≥ 3 half-lives for monoclonal antibodies or ≥ 5 half-lives for other non-cytotoxic agents (whichever is longer).
3. Subjects on anticoagulant or antiaggregant (including low-dose aspirin) therapy at screening for concomitant medical conditions should be evaluated in coordination with their cardiologist for the benefit/risk ratio of continuing their anticoagulant or antiaggregant therapy during the study due to the potential increased risk of bleeding in the event of occurrence of severe thrombocytopenia. Blood cell count should be performed more frequently in such subjects, at least weekly throughout study, and more often in cases of grade 2 to 3 thrombocytopenia.

Prohibited

Listed below are specific restrictions for concomitant medications / therapy during the course of the trial:

1. Concurrent treatment with any investigational drug or anticancer (antineoplastic) therapy, including the following: chemotherapy, immunotherapy, hormone therapy, or biological therapies.

   (The only exception is hydroxyurea given to control hyperleukocytosis that can be continued until 48 hours before MK-8268 treatment initiation, but must be stopped at that time. Furthermore, should a rapidly increasing white blood cell count occur during the first cycle of MK-8268 treatment, hydroxyurea should not be given earlier than day cycle 1 / day 3, nor beyond day 43 (cycle 3 / day 1), and for the shortest period possible as clinically indicated to control hyperleukocytosis and maintain the subject on study. On day 43 (cycle 3 / day 1), the decision to start MK-8268 for cycle 3 will be made by the investigator according to the subject's anticipated benefit. If hydroxyurea has to be resumed during cycle 3, this will be considered as MK-8268 treatment failure, and the subject will be withdrawn from the study)
2. Corticosteroids (except chronic treatment with ≤ 4.0 to 6.0 mg / day of methylprednisolone or equivalent dose of other corticosteroids).
3. Prophylactic antiemetic drugs or other drugs given with a prophylactic intent in the first cycle (unless the Early Phase Safety Teleconferences Meeting decides to deliver systematic premedication).
4. Strong inducers, strong inhibitors, and sensitive / narrow therapeutic range substrates of the P450 cytochrome enzymes CYP3A4 and CYP2A6 (see Section 12.9) are prohibited. Moderate inducers and moderate inhibitors of these cytochrome enzymes should be used with caution. Since this list is not comprehensive, the investigator should use his/her medical judgment when a subject presents with a medication not on the list or call the Sponsor Clinical Director for clarification.

5.6 Rescue Medications & Supportive Care

No rescue or supportive medications are specified to be used in this trial.

5.6.1 Supportive Care Guidelines

Toxicities will be managed by the investigator according to the local standard of care, except where noted in this protocol. Supportive treatment must be reported in the concomitant medication section of the eCRF.

5.6.1.1 General Guidelines for Clinically Significant Toxicities

General guidelines regarding management and dose reduction for adverse events that are considered by the investigator to be related to study treatment are provided in Section 5.2.1.5. All adverse events should be monitored closely, with supportive care provided according to institutional standards.

5.6.1.2 Hepatic Laboratory Abnormalities

All trial subjects with liver test abnormalities should be followed weekly until all abnormalities return to normal or to the baseline state. For subjects with isolated total bilirubin increases > 2X ULN or 2X baseline (if elevated at baseline), monitoring should be every 2 weeks until bilirubin returns to normal or to the baseline state. DILI may develop or progress even after the causative drug has been stopped. Results should be recorded on the case report form and in the database. See Section 12.8 for guidelines on the handling of these events (potential Hy's law cases).

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

Subjects must avoid drinking grapefruit juice while on study, as this is a CYP3A4 inhibitor and is therefore not permitted. Subjects should otherwise maintain a normal diet, except when required to fast prior to MK-8628 administration (Section 5.2.2), or unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

5.7.2 Potential Phototoxicity

No phototoxicity studies have been performed in humans to date. However, as MK-8628 absorbs light in the range of 290 and 400 mm with a molar extinction coefficient (MEC) of > 1,000 L/mol.cm, it is recommended that subjects avoid the sun and UV exposure until the results of phototoxicity studies are available.

5.7.3 Contraception

MK-8628 may have adverse effects on a fetus in utero. Furthermore, it is not known if MK-8628 has transient adverse effects on the composition of sperm.

For this trial, male subjects will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Female subjects will be considered of non-reproductive potential if they are either:

1) postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR

2) have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy, or bilateral tubal ligation/occlusion at least 6 weeks prior to screening;

OR

3) has a congenital or acquired condition that prevents childbearing.

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug MK-8628 and for 90 days after the last dose of study drug. Subjects must comply with one of the following:

1) practice abstinence† from heterosexual activity;

OR

2) use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are‡:

Single method (one of the following is acceptable):

- intrauterine device (IUD)
- vasectomy of a female subject's sole male partner
- contraceptive rod implanted into the skin

Combination method (requires use of two of the following):

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

†Abstinence (relative to heterosexual activity) can 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 ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) 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.

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, subjects of childbearing potential must adhere to the contraception requirement

(described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication treatment [Day 1] for oral contraception) throughout the study period up to 90 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

Monthly pregnancy testing is recommended per local standards if applicable.

For countries (e.g., Sweden and Norway) or sites that follow the Clinical Trial Facilitation Group (CTFG) guidance, please use the following:

MK-8628 may have adverse effects on a fetus in utero. Furthermore, it is not known if it may have transient adverse effects on the composition of sperm. Therefore, non-pregnant, non-breastfeeding women may only be enrolled if they are willing to follow the CTFG Guidance (Final Version 2014-09-15, Sections 4.1 and 4.2) for highly effective birth control as outlined below, or are considered to be highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. Subjects should use birth control methods that can achieve a failure rate of less than 1% per year when used consistently and correctly and are considered as highly effective birth control methods. Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
    - Oral
    - Intravaginal
    - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
    - Oral
    - Injectable
    - Implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomised partner

- Sexual abstinence

Subjects should start using birth control from study Visit 1 throughout the study period up to 90 days after the last dose of study therapy.

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in Section 7.2.2 – Reporting of Pregnancy and Lactation to the Sponsor. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.7.4 Pregnancy

If a subject inadvertently becomes pregnant while on treatment with MK-8628, the subject will immediately be discontinued from trial treatment. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the SPONSOR without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the SPONSOR. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the SPONSOR and followed as described above and in Section 7.2.2.

5.7.5 Nursing Women

It is unknown whether MK-8628 is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

5.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal procedures; including specific details regarding withdrawal from Future Biomedical Research, are provided in Section 7.1.4 – Other Procedures.

Subjects will continue study treatment until any of the following events at which point it will be definitively discontinued:

- Disease progression
- Unacceptable toxicity

- Subject withdrawal of consent
- Subject non-compliance
- Treatment interruption for > 2 weeks for any reason (except in the event of perceived benefit, with Sponsor agreement)
- Recurrence of DLT despite dose reduction (except in the event of perceived benefit, with Sponsor agreement)

However, in case of investigator's perceived benefit for the subject, treatment continuation can be considered with dose reduction despite delay/interruption > 2 weeks or reoccurrence of a DLT with the same intensity after one dose reduction. The perceived benefit of the investigator is defined by 1) any objective tumor response, or 2) any tumor regression not meeting standard response criteria, but which could improve with additional treatment, or 3) any symptomatic improvement, which, in the investigator's opinion, could not be achieved by other means. If, in the cases described above, DLT recurs with the same intensity despite one dose reduction, a second dose reduction may be considered. The decision should be discussed with the Sponsor, but the final decision must be made by the investigator. The reason for and date of dose reduction must be recorded in the eCRF and source documented in the subject's medical records.

In all cases, the reason for and date of study treatment discontinuation must be recorded in the eCRF and source documented in the subject's medical records. As far as possible, there should be only one reason for treatment discontinuation. If there are several (e.g. concomitant progressive disease and toxicity), the primary one must be reported. The subject must be followed up to establish whether the reason was an AE, and if so, this must be reported as such.

As far as possible, all examinations scheduled for the final study day must be performed for all subjects who receive the investigational product but who do not complete the study according to protocol.

The investigator must make every effort to contact subjects lost to follow-up, especially when a subject is treated in another non-study center.

5.9 Subject Replacement Strategy

Subjects not evaluable for DLT (i.e. receiving less than 85% of the intended cumulative dose in Cycle 1 for any reason other than toxicity; < 18 days of treatment) and who do not experience DLT will be replaced.

A subject who discontinues from the trial for any other reason will not be replaced.

5.10 Beginning and End of the Trial

The overall trial begins when the first subject signs the informed consent form. The overall trial ends when the last subject completes the last study-related phone-call or visit, discontinues from the trial or is lost to follow-up (i.e. the subject is unable to be contacted by the investigator).

5.11 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1. Incidence or severity of adverse drug reactions in this or other trials suggest a potential health hazard to subjects
2. Quality or quantity of data recording is inaccurate or incomplete
3. Poor adherence to protocol and regulatory requirements
4. Plans to modify or discontinue the development of the study drug

In the event of Sponsor decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made

6.0 TRIAL FLOW CHART

	Screening Phase	**Treatment Phase Cycle = 21 days**							**End of Treatment**	**Post Treatment Phase**		
Treatment Cycle/Title:	Pre-study / Screening (Visit 1)	Cycle 1			Cycle 2	Cycle 3	Cycle 4	Cycle 5 and beyond	Treatment Discontinuation Visit	30 Day Post Treatment Safety Follow-up Visit	Follow-up Visits (AML)[a]	Follow-up Visits (DLBCL)[a]
Cycle Day:		1	8	15	1	1	1	1	At the time of discontinuation	30 days post discontinuation	Every 6 weeks post discontinuation	Every 12 weeks post discontinuation
Scheduling Window Days:	-14 to -1		±3	±3	±3	±3	±3	±3		±3	±3	±7
Administrative Procedures												
Informed Consent	X											
Informed Consent for Future Biomedical Research	X											
Inclusion/Exclusion Criteria	X											
Subject Identification Card	X											
Demographics, Medical History	X											
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X		
Diagnosis & prior treatments for malignancy	X											
Baseline symptoms & complaints	X											
MK-8628 Administration/Dispensing												
MK-8628 Administration/Dispensing		BID continuously[b] at assigned dose level; Study drug will be dispensed on or prior to day 1 of each cycle.										
Clinical Procedures/Assessments												
Full Physical Examination	X	X							X			
Directed Physical Examination			X	X	X	X	X	X				
ECOG Performance Status (PS)	X	X	X	X	X	X	X	X	X			

	Screening Phase	**Treatment Phase Cycle = 21 days**							**End of Treatment**	**Post Treatment Phase**		
Treatment Cycle/Title:	Pre-study / Screening (Visit 1)	Cycle 1			Cycle 2	Cycle 3	Cycle 4	Cycle 5 and beyond	Treatment Discontinuation Visit	30 Day Post Treatment Safety Follow-up Visit	Follow-up Visits (AML)[a]	Follow-up Visits (DLBCL)[a]
Cycle Day:		1	8	15	1	1	1	1	At the time of discontinuation	30 days post discontinuation	Every 6 weeks post discontinuation	Every 12 weeks post discontinuation
Scheduling Window Days:	-14 to -1		±3	±3	±3	±3	±3	±3		±3	±3	±7
Height	X											
Weight	X	X	X	X	X	X	X	X	X			
Vital Signs (heart rate, blood pressure, temperature)	X	X[c]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X	X[n]		
12 Lead Electrocardiogram (ECG)	X	X[c]				X[d]		X[e]	X	X[n]		
Bone Marrow Aspiration / Biopsy: AML[f]	X				X	X						
Tumor Assessment & Response Evaluation: AML[f]					X	X	X	X	X		X[a]	
PET & CT Imaging (Neck, Chest, Abdomen, Pelvis): DLBCL[g]	X							X	X[h]			X[a]
Tumor Assessment & Response Evaluation: DLBCL[g] and Assessment of Lymphoma B Symptoms[g]								X	X[h]			X[a]
Adverse Events Monitoring	X	X	X	X	X	X	X	X	X	X[i]	X[i]	X[i]
Tumor Sample Submission [j]	X											
Laboratory Procedures/Assessments												
Complete Blood Count (CBC) [k]	X[m]	X	X	X	X	X	X	X	X	X[n]	X[a]	
PT-International Normalized Ratio (INR), aPTT, and Factor VII	X[m]	X	X	X	X	X	X	X	X	X[n]		
Serum Chemistry [l]	X[m]	X	X	X	X	X	X	X	X	X[n]		
Urinalysis	X	X	X	X	X	X	X	X	X	X[n]		

	Screening Phase	**Treatment Phase Cycle = 21 days**							**End of Treatment**	**Post Treatment Phase**		
Treatment Cycle/Title:	Pre-study / Screening (Visit 1)	Cycle 1			Cycle 2	Cycle 3	Cycle 4	Cycle 5 and beyond	Treatment Discontinuation Visit	30 Day Post Treatment Safety Follow-up Visit	Follow-up Visits (AML)[a]	Follow-up Visits (DLBCL)[a]
Cycle Day:		1	8	15	1	1	1	1	At the time of discontinuation	30 days post discontinuation	Every 6 weeks post discontinuation	Every 12 weeks post discontinuation
Scheduling Window Days:	-14 to -1		±3	±3	±3	±3	±3	±3		±3	±3	±7
Urine or Serum Pregnancy Test – if applicable[o]	X[o]											
PK Blood Sampling		X[p]	X[q]	X[q]	X[q]							
PD Blood Sampling		X[r]	X[s]									
Blood for Genetic Analysis [t]		X										

a. In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status every 6 weeks (± 3 days) for AML subjects and every 12 weeks (± 7 days) for DLBCL subjects until (1) the start of new anti-cancer treatment, (2) documented disease progression, (3) death, or (4) the end of the study, whichever occurs first. If subjects have stable disease, partial response, or complete response, they should continue on this assessment schedule. Tumor response assessments should occur at any time where there is clinical suspicion of progression or relapse.

b. MK-8628 is to be administered orally with water in a fasted state, and as part of a BID regimen (twice daily, approximately 12 hours apart). Subjects should not have food for 1 hour before or 3 hours after study drug administration. Dosing not performed at the same time (±2h) as on other days should be skipped. Subjects are to be instructed that if they vomit or omit their dose in that time frame, it is not to be replaced.

c. Collected at the following time points on day 1 of cycle 1: pre-dose, 1 hour post-dose, 2 hours post-dose.

d. Collected prior to the subject dosing (pre-dose) on that day.

e. Collected prior to the subject dosing (pre-dose) on day 1 of every odd treatment cycle (every 6 weeks) after cycle 3 day 1.

f. AML tumor response assessments will be completed through the analysis of bone marrow aspiration samples and bone marrow biopsy samples (if necessary). See Section 7.1.2.7.1. Bone marrow analysis is required at screening, cycle 2 day 1, and cycle 3 day. Tumor response assessments will be conducted on day 1 of every cycle beyond cycle 3 through hematological analysis of peripheral blood. Evidence of response in peripheral blood may be confirmed by further bone marrow assessments as displayed in the tumor response criteria. The timing of tumor response assessments should follow calendar days and should not be adjusted for delays in cycle starts.

g. DLBCL tumor response assessments will be completed through PET-CT and CT imaging analysis. See Section 7.1.2.7.2. The timing of tumor response assessments should follow calendar days and should not be adjusted for delays in cycle starts. The same imaging technique should be used in a subject throughout the trial. Routine imaging assessments (or bone marrow biopsy) performed outside of the scope of this study will be acceptable to complete the response criteria for DLBCL at screening, if performed ≤ 4 weeks prior to study entry. Assessment of lymphoma B symptoms should occur with each lymphoma disease response assessment.

h. In subjects with an unconfirmed PD assessment, a radiological assessment should be performed at the time of treatment discontinuation. If previous scan was obtained within 4 weeks prior to the date of discontinuation, then a repeat scan at treatment discontinuation isn't mandatory. However, imaging should occur at any time where there is clinical suspicion of progression.
i. Record all AEs occurring within 30 days after the last dose of trial treatment regardless when the Treatment Discontinuation Visit occurs. After 30 days, any drug related AE regardless of seriousness occurring outside of any reporting timeframes must be reported.
j. Submission of tumor samples is applicable to subjects that sign the Future Biomedical Research consent form. A fresh bone marrow aspiration sample is required for AML subjects, in addition to a bone marrow trephine sample (if available). If a bone marrow trephine sample was not obtained (because not needed or unable to perform) or the bone marrow trephine sample is inadequate/poor quality, then only a bone marrow aspirate sample should be submitted. An archived or fresh lymph node biopsy sample without invasive procedure (e.g. superficial lymph node) is required for DLBCL subjects. If an archived lymph node sample is not available, the subject must agree to undergo a fresh tumor biopsy. All tumor biopsy samples will be sent to a central laboratory for further analysis.
k. In cases of grade > 2 hematologic toxicity CBC will be performed twice a week until recovery to grade ≤ 2. In cases of neutropenia/thrombocytopenia grade 4, CBC will be performed at least every other day until recovery to grade ≤ 3. In cases of fever ≥ 38 °C, infection, purpura, or bleeding, additional CBC should be done as clinically indicated. In addition, bone marrow aspiration will be performed in all subjects with grade 4 thrombocytopenia lasting > 3 days.
l. See Section 7.1.3, from cycle 3 on, in the absence of ≥ grade 2 abnormalities, these tests will be performed every cycle, otherwise they are to be done weekly until resolution to baseline levels or < grade 2.
m. Screening CBC, PT-International Normalized Ratio (INR), aPTT, Factor VII and serum chemistry measurements must be taken within 7 days of the first dose of study treatment.
n. Unresolved abnormal assessments that are drug related AEs should be followed until resolution.
o. For women of reproductive potential, urine pregnancy test must be confirmed negative within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. The subject must be excluded in the event of a positive or borderline-positive serum test result.
p. PK blood samples will be collected at pre-dose (before drug intake), 20 minutes post-dose (±5 min), 1 hour post-dose (±10 min), 2 hours 15minutes post-dose (±10 min), 3hours15minutes post-dose (±10 min), 8 hours post-dose (± 1 hour), and 12 hours post-dose (± 2 hours, before the second daily dose on day 1).
q. PK blood samples will be collected at pre-dose (before drug intake).
r. PD blood samples will be collected at pre-dose (before drug intake), 3 hours 15 minutes post-dose (±10 min), 8 hours post-dose (± 1 hour), and 12 hours post-dose (± 2 hours, before the second daily dose on day 1).
s. PD blood samples will be collected at pre-dose (before drug intake).
t. Details for collection can be found in Section 7.1.3 Laboratory Procedures/Assessments.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The investigator or qualified designee must obtain documented consent from each potential subject or each subject's legally acceptable representative prior to participating in a clinical trial or Future Biomedical Research. If there are changes to the subject's status during the trial (e.g., health or age of majority requirements), the investigator or qualified designee must ensure the appropriate consent is in place.

7.1.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the Future Biomedical Research consent to the subject, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the Future Biomedical Research sub-trial. A copy of the informed consent will be given to the subject.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

7.1.1.3 Subject Identification Card

All subjects will be given a Subject Identification Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the subject with a Subject Identification Card immediately after the subject provides written informed consent. At the time of treatment allocation/randomization, site personnel will add the treatment/randomization number to the Subject Identification Card.

The subject identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about trial medication/vaccination in emergency situations where the investigator is not available.

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. A detailed medical history must be documented, including:

- non-cancer medical history
- concurrent illnesses
- demographics
- diagnosis and prior treatments for malignancies

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 4 weeks or 5 half-lives before first dose of trial medication.

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial.

7.1.1.6 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to randomization or treatment allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

Specific details on the screening visit requirements (screening/rescreening) are provided in Section 7.1.5.1.

7.1.1.7 Assignment of Treatment/Randomization Number

All eligible subjects will be allocated, by non-random assignment, and will receive a treatment/randomization number. The treatment/randomization number identifies the subject for all procedures occurring after treatment allocation/randomization. The assigned screening number will become the subjects' treatment allocation number. Once a treatment/randomization number is assigned to a subject, it can never be re-assigned to another subject.

A single subject cannot be assigned more than 1 treatment/randomization number.

7.1.1.8 Trial Compliance

Administration of the investigational product will be supervised by the investigator. Any delegation of this responsibility must be documented.

In practice, on study visit days study nurses will supervise the intake of the appropriate MK-8628 dose, explaining to subjects the exact number of capsules they should take. Nurses will document in the eCRF the administration, the dose, the time of administration, as well as any immediate reactions at the time of intake.

For non-visit days, MK-8628 will be taken at home. Subjects will record daily in a specific diary, the number of capsules swallowed, time of intake, as well as possible reactions, including vomiting, and their date/time of occurrence.

When a subject attends a study visit, he/she will bring any unused capsules and their diary. According to the center procedures, the diary will be used to complete the eCRF treatment administration section, either directly as a Source Document or as an aid for completing the nurse's notes which will be used as a Source Document.

Interruptions from the protocol specified treatment > 2 weeks require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0. Toxicities will be characterized in terms including seriousness, causality, toxicity grading and action taken with regard to trial treatment.

Please refer to Section 7.2 for detailed information regarding the assessment and recording of AEs.

7.1.2.2 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant findings should be recorded as medical history. After the first dose of trial treatment, new clinically significant abnormal findings should be recorded as AEs. A final full physical exam should be completed during the end of treatment visit.

7.1.2.3 Directed Physical Exam

For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration. New clinically significant abnormal findings should be recorded as AEs.

7.1.2.4 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or designee will assess the ECOG status (see Section) at screening, prior to trial administration on Day 1 of each cycle, and during the post-treatment follow-up period.

7.1.2.5 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to trial administration on day 1 of each cycle, and during the treatment discontinuation visit as specified in the Trial Flow Chart. Vital signs include heart rate, blood pressure, body temperature, and weight.

7.1.2.6 12 Lead Electrocardiogram (ECG)

The investigator or qualified designee will take 12 lead ECGs as specified in the Trial Flow Chart. ECGs collected on cycle 1 day 1 should be taken at the following time points:

- Pre-dose
- 1 hour post-dose
- 2 hours post-dose

After cycle 1, ECGs should be collected on day 1 of every odd cycle (every 6 weeks) at the pre-dose (prior to dosing) time point.

7.1.2.7 Tumor Assessment / Response Evaluation

Tumor response should be assessed on the cycle days depicted in section 6.0, and based on the criteria displayed in Sections 7.1.2.7.1 and 7.1.2.7.2.

7.1.2.7.1 Bone Marrow Aspiration / Biopsy & Criteria for Response Assessment - AML

The anti-tumor activity of MK-8628 will be evaluated as part of the efficacy endpoints using the following criteria:

- Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet (Döhner et al, *Blood*, 2010)] See Appendices 12.4.

These International Working Group criteria will be applied by the site as the primary measure for assessment of disease response and as a basis for all protocol guidelines related to disease status (e.g. discontinuation of study therapy). The assessments will be completed through analysis of bone marrow aspiration samples, and bone marrow biopsy samples (if necessary). The timing for tumor response assessments should follow calendar days and should not be adjusted for delays in cycle starts.

Tumor assessment and response evaluation should be completed at the following visits:

- Screening
- Cycle 2 day 1 (± 3 days)
- Cycle 3 day 1 (± 3 days)
- *Beyond Cycle 3
- Treatment Discontinuation Visit

**Follow-up Visits (every 6 weeks post-treatment, ± 3 days)*Response assessments will be conducted on day 1 of every cycle (± 3 days) beyond cycle 3 through hematological analysis of peripheral blood. Evidence of response or progression in peripheral blood may be confirmed by further bone marrow assessments as displayed in Section 12.4.

**In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status every 6 weeks (± 3 days) until (1) the start of new anti-cancer treatment, (2) documented disease progression, (3) death, or (4) the end of the study, whichever occurs first. If subjects have stable disease, partial response, or complete response, they should continue on this assessment schedule. Tumor response assessments should occur at any time where there is clinical suspicion of progression.

7.1.2.7.2 Positron Emission Tomography (PET), Computed Tomography (CT), & Criteria for Response Assessment - DLBCL

The anti-tumor activity of MK-8628 will be evaluated as part of the efficacy endpoints using the following International Working Group criteria:

- 5 Point-Scale per the Lugano Classification (Cheson et al, *J Clin Oncol, 2014*) [46] See Appendices 12.5.

These International Working Group criteria will be applied by the site as the primary measure for assessment of disease response and as a basis for all protocol guidelines related to disease status (e.g. discontinuation of study therapy). The assessments will involve the use of PET-CT and CT imaging (PET based response to analyze FDG-avid uptake using a 5 point scale, and confirm residual vs. metabolically active tumor locations). The timing of tumor response assessments should follow calendar days and should not be adjusted for delays in cycle starts. The same imaging technique should be used in a subject throughout the trial. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility and for subject management. The sponsor may potentially collect radiologic assessments for retrospective analysis by a central vendor. Assessment of lymphoma B symptoms should occur with each lymphoma disease response assessment.

The tumor response assessments should be completed at the following visits:

- *Screening
- Cycle 5 day 1 (Week 12, ± 3 days) and every 12 weeks thereafter (± 3 days)
- ** Treatment Discontinuation Visit
- ***Follow-up Visits (every 12 weeks post-treatment, ± 7 days)

*Routine imaging (or bone marrow biopsy) performed outside of the scope of this study will be acceptable to complete the criteria for response assessment at screening, if performed ≤ 4 weeks prior to study entry.

**In subjects with an unconfirmed PD assessment, a radiological assessment should be performed at the time of treatment discontinuation. If previous scan was obtained within 4 weeks prior to the date of discontinuation, then a repeat scan at treatment discontinuation isn't mandatory. However, imaging should occur at any time where there is clinical suspicion of progression.

***In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status every 12 weeks (± 7 days) until (1) the start of new anti-cancer treatment, (2) documented disease progression, (3) death, or (4) the end of the study, whichever occurs first. If subjects have stable disease, partial response, or complete response, they should continue on this assessment schedule. Tumor response assessments should occur at any time where there is clinical suspicion of progression.

7.1.2.8 Tumor Sample Submission

A tumor biopsy sample must be collected for the purpose of predictive biomarker analysis, and submitted to the central laboratory within the 14 day screening window. Additional details can be found in the trial specific laboratory manual.

7.1.2.8.1 Bone Marrow Aspiration (AML Subjects)

A fresh bone marrow aspiration sample is required for AML subjects, in addition to a bone marrow trephine sample (if available). If a bone marrow trephine sample was not obtained (because not needed or unable to perform) or the bone marrow trephine sample is inadequate/poor quality, then only a bone marrow aspirate sample should be submitted.

This sample collection procedure should occur during the tumor response assessment required at screening (Section 7.1.2.7.1).

7.1.2.8.2 Lymph Node Biopsy (DLBCL Subjects)

Archival or fresh superficial lymph node biopsy samples are required from subjects during screening. The sample should be a formalin-fixed paraffin embedded (FFPE) tumor biopsy sample or newly obtained core or excisional biopsy [fine needle aspiration (FNA) is not adequate] to be submitted for characterization at a central laboratory. If an archived sample is not available, the subject must agree to undergo a fresh tumor biopsy. Submission of FFPE tumor tissue sample blocks is preferred.

Biopsy samples (archival or newly obtained) may be used for confirmation of diagnosis.

Biopsy of lesions on study should be limited to non-target lesions or new lesions if their pathologic etiology is ambiguous, and the tissue sample should have proper size to enable multiple planned biomarker analyses but not artificially decrease the longest diameter of the lesion. If a tumor biopsy was of a target lesion during eligibility assessment, it is preferred to obtain a new baseline scan.

- **Newly Obtained Tumor Tissue**

This sample should be sent to the central laboratory in formalin (strongly preferred) or as a formalin-fixed paraffin embedded (FFPE) block. If approved by the Sponsor, unstained/freshly cut slides cut from FFPE tissue block may be accepted.

- **Archival Tumor Tissue (if available)**

Archival tissue sample should be provided in the form of formalin-fixed paraffin embedded (FFPE) tissue block (preferred). If approved by the Sponsor, unstained/freshly cut slides cut from FFPE tissue block may be accepted.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in the Procedures Manual. .

7.1.3.1 Laboratory Safety and Other Evaluations (Hematology, Chemistry, Urinalysis, and Other)

Laboratory tests for hematology, chemistry, urinalysis, and other are specified in Table 7.

Table 7 Laboratory Tests

Hematology	Chemistry	Urinalysis[b]	Other
• Complete Blood Count (CBC): ✓ White Blood Cell (WBC) Count ✓ WBC Differential ✓ Red Blood Cell (RBC) Count ✓ Hemoglobin ✓ Hematocrit ✓ Platelet Count ✓ Mean Corpuscular Volume (MCV) ✓ Mean Corpuscular Hemoglobin Concentration (MCHC) ✓ Red Cell Distribution Width (RDW) ✓ Reticulocyte Count ✓ Mean Platelet Volume (MPV) ✓ Platelet Distribution Width (PDW) • Prothrombin Time (PT) / International Normalized Ratio (INR) • Activated Partial Thromboplastin Time (aPTT) • Factor VII	• Albumin • Alkaline phosphatase • Alanine aminotransferase (ALT) • Aspartate aminotransferase (AST) • Carbon dioxide (CO2 or bicarbonate)[b] • Calcium • Chloride • Creatinine[c] • Glucose • Lactate dehydrogenase (LDH) • Phosphorus • Potassium • Sodium • Total Bilirubin • Direct Bilirubin, if total bilirubin is elevated above the upper limit of normal • Total protein • Blood Urea Nitrogen (BUN) or Urea	• Blood • Glucose • Protein • Specific gravity • Microscopic exam, if abnormal results are noted	• Serum β-human chorionic gonadotropin (β-hCG)[a] • Urine Pregnancy Test[a]

[a] Perform on women of childbearing potential only. Urine pregnancy test is preferred. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
[b] If these tests are not done per local institutional standards as part of standard of care in a geographical region then these tests do not need to be performed.
[c] For subjects with a baseline calculated creatinine clearance below the normal institutional laboratory range, a baseline measured creatinine clearance should be performed.

7.1.3.1.1 Complete Blood Count

In cases of grade > 2 hematologic toxicity, CBC will be performed twice a week until recovery to grade ≤ 2. In cases of neutropenia/thrombocytopenia grade 4, CBC will be performed at least every other day until recovery to grade ≤ 3. In addition, in cases of thrombocytopenia grade 4 lasting > 3 days, a bone marrow aspiration is to be performed. In cases of fever ≥ 38 °C, infection, purpura or bleeding, additional CBC should be done as clinically indicated.

7.1.3.1.2 Serum Chemistry

From cycle 3 on, in the absence of ≥ grade 2 abnormalities, these tests will be performed every cycle, otherwise they are to be done weekly until resolution to baseline levels or < grade 2.

7.1.3.1.3 Urine or Serum β-hCG

All women who are being considered for participation in the study, and who are not surgically sterilized or postmenopausal, will be tested for pregnancy via a urine test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. The subject must be excluded in the event of a positive or borderline-positive serum test result.

7.1.3.2 Pharmacokinetic/Pharmacodynamic Evaluations

7.1.3.2.1 PK Sample Collection (Plasma)

Samples will be collected on day 1 and three additional steady-state trough concentrations will be collected 1, 2 and 3 weeks after the first treatment intake.

The timing of the PK sample collections is as follows (see also Table 8 below). Seven blood samples will be collected on **Day 1 of Cycle 1**: immediately prior to the first dose (**T0**) and **20 min**±5min, **1h**±10min, **2h15min**±10min, **3h15min**±10min, **8h**±1h, and **12h**±2 hours (immediately before the second daily dose on day 1). Subjects will either remain in the clinical research unit (CRU), or be hospitalized, for a minimum of 12±2hours hours for PK sampling on day 1.

In addition, a single blood sample will be collected from all subject immediately before drug intake on **days 8** (±1 days), **15** (±2 days), **and 22** (±3 days) to evaluate steady-state trough concentrations. Note: On these three days, it is critical that the subject withhold the morning dose until after the PK sample is collected in the clinic. Every effort should be made to collect the sample approximately 12h after the previous evening dose. The timing of the previous dose should be recorded. See Table 8.

Table 8 PK Sample Collection Timing

PK Sample #	Visit	Time of collection
1	Cycle 1 Day 1	T0: Pre-morning dose
2	Cycle 1 Day 1	20 min ±5 min post-morning dose
3	Cycle 1 Day 1	1 hr ±10 min post-morning dose
4	Cycle 1 Day 1	2 hr 15 min ±10 min post-morning dose
5	Cycle 1 Day 1	3 hr 15 min ±10 min post-morning dose
6	Cycle 1 Day 1	8 hr ±1 hr post-morning dose
7	Cycle 1 Day 1	12 hr ± 2 hours post-morning dose
8	Cycle 1 Day 8	Pre-morning dose
9	Cycle 1 Day 15	Pre-morning dose
10	Cycle 1 Day 22 *(Cycle 2 Day 1)*	Pre-morning dose

In total, ten blood samples of 3.0 mL each will be collected, i.e. approximately 30 mL of blood will be drawn per subject treated in the BID regimen from a peripheral venous access for PK analysis.

Sample collection, storage and shipment instructions for plasma samples will be provided in the Procedure Manual.

7.1.3.2.2 PK Assay Method and Parameters Analyzed

Plasma concentrations of MK-8628 will be measured using Ultra Performance Liquid Chromatography with tandem Mass Spectrometry detection (UPLC-MS/MS).

The following parameters will be determined as appropriate, and may include trough (C_{min}) and peak (C_{max}) concentrations, T_{max}, AUC[0-∞], Vd_{ss}, t1/2, steady state, total clearance (CL) if non-compartmental analysis is performed.

PK data for MK-8628 will be interpreted in terms of safety findings and compared with historical data.

7.1.3.2.3 PD Sample Collection

A range of PD biomarkers (based on current PD knowledge) will be explored in all subjects treated, using appropriate assays.

The timing of the PD sample collections is as follows (see also Table 9 below), and timing of collections should align with the collection of the PK samples at the same timepoints described in Table 9. PD biomarkers will be analyzed in peripheral blood. Four blood samples will be collected on **Day 1 of Cycle 1**: immediately prior to the first dose (**T0**) and **3h15min**±10min, **8h**±1h, and **12h**±2 hours (immediately before the second daily dose on day 1). In addition, a single blood sample will be collected from all subjects immediately before drug intake on **day 8** (±1 day)(same day as PK sample collection). See Table 9.

Table 9 PD Sample Collection Timing

PD Sample #	Visit	Time of collection
1	Cycle 1 Day 1	T0: Pre-morning dose
2	Cycle 1 Day 1	3 hr 15 min ±10 min post-morning dose
3	Cycle 1 Day 1	8 hr ±1 hr post-morning dose
4	Cycle 1 Day 1	12 hr ±2 hours post-morning dose
5	Cycle 1 Day 8	Pre-morning dose

7.1.3.3 Planned Genetic Analysis Sample Collection

This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. If there is either a documented law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes, then this sample will not be collected at that site. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consent. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

Sample collection, storage and shipment instructions for plasma samples will be provided in the Procedure Manual.

7.1.3.4 Future Biomedical Research Sample Collection

The following specimens are to be obtained as part of Future Biomedical Research:

DNA for future research.

- Leftover main study tumor (bone marrow samples) stored for future research (AML subjects)
- Archived or fresh lymph node samples for future research (DLBCL subjects)

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the Treatment Discontinuation Visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events.

7.1.4.1.1 Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com), and a form will be provided by the Sponsor to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from the Sponsor to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject’s personal information and their specimens. In this situation, the request for specimen destruction cannot be processed.

7.1.4.2 Blinding/Unblinding

This is an open label trial; there is no blinding for this trial.

7.1.4.3 Domiciling

Subjects will report to the clinical research unit (CRU) the morning of the scheduled day of trial drug administration in Cycle 1 and remain in the unit for a minimum of 12±2 hours post-dose to collect PK blood samples and check vital signs, when appropriate. It is recommended, but not required, that subjects be admitted overnight for this first treatment day (Cycle 1 Day 1), and at the discretion of the investigator, subjects may be requested to remain in the CRU longer.

7.1.4.4 Calibration of Critical Equipment

The investigator or qualified designee has the responsibility to ensure that any critical device or instrument used for a clinical evaluation/test during a clinical trial that provides important information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the trial site.

Critical Equipment for this trial includes:

- Laboratory equipment
- Imaging equipment
- Other equipment (exg: 12 Lead ECG Machines)
- See protocol-specified guidance in the Administrative Binder, Procedures Manual, and Site Imaging Manual.

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5.1 Screening

Each candidate subject will be examined before starting the study to determine eligibility for participation as set forth in Section 5.1. This must be done within 2 weeks prior to the first study treatment administration (exceptions listed below). Screening procedures may be repeated after consultation with the Sponsor.

Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame.

Screening procedures are to be performed within 2 weeks prior to the first dose of trial treatment except for the following:

- For women of reproductive potential, a urine or serum pregnancy test will be performed within 72 hours prior to the subject's first dose of trial treatment on cycle 1 / day 1.

- The following assessments need to be completed within a 7 day window (day -7 to day -1) prior to the subject's first dose of trial treatment on cycle 1 / day 1:
    - Complete Blood Count (CBC)
    - PT-International Normalized Ratio (INR), aPTT, and Factor VII
    - Serum Chemistry
- The following is applicable to DLBCL subjects only: routine imaging (or bone marrow biopsy) performed outside of the scope of this study will be acceptable to complete the Response Criteria for Malignant Lymphoma (Section7.1.2.7.2) at screening, if performed ≤ 4 weeks prior to study entry.

7.1.5.2 Treatment Period

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5.3 End of Treatment

All subjects will complete a treatment discontinuation visit at the time of MK-8628 treatment withdrawal, or within 3 days of last dose.

7.1.5.4 Post-Treatment

7.1.5.4.1 30 Day Safety Follow-up

After the last treatment administration, subjects will be followed up for safety for 30 days and then until resolution of any AEs for which a relationship to MK-8628 cannot definitely be excluded (or categorized as sequelae). A safety follow-up visit will be performed 30 days (±5 days) after the last MK-8628 intake.

7.1.5.4.2 Additional Follow-up

In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status every 6 weeks (± 3 days) for AML subjects and every 12 weeks (± 7 days) for DLBCL subjects until (1) the start of new anti-cancer treatment, (2) documented disease progression, (3) death, or (4) the end of the study, whichever occurs first. If subjects have stable disease, partial response, or complete response, they should continue on this assessment schedule. Tumor response assessments should occur at any time where there is clinical suspicion of progression or relapse.

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-

specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Sponsor's product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

Adverse events may occur during clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Progression of the cancer under study is not considered an adverse event unless it is considered to be drug related by the investigator

All adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of treatment allocation/randomization through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Electronic reporting procedures can be found in the Electronic Data Capture (EDC) data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Adverse events will not be collected for subjects during the pre-screening period (for determination of archival tissue status) as long as that subject has not undergone any protocol-specified procedure or intervention. If the subject requires a blood draw, fresh tumor biopsy etc., the subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting.

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for MK-8628 by 1 dose in a 24 hour time period (i.e. $\geq$ 3 total doses in 24 hrs). No specific information is available on the treatment of overdose of MK-8628. In the event of overdose, MK-8628 should be discontinued and the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with ("results from") the overdose of Sponsor's product or vaccine, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Sponsor's product or vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations that occur from the time of treatment allocation/randomization through 30 days following cessation of Sponsor's product must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial.

Pregnancies and lactations of subjects and female partners of male subjects from the time the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations of subjects and female partners of male subjects that occur from the time of treatment allocation/randomization through 30 days following cessation of Sponsor's product must be reported. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign

hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event.

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.

- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose.

Refer to Table 10 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (reference Section 7.2.3.3 for additional details), that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 30 days following cessation of treatment, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (reference Section 7.2.3.3 for additional details), whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to the Sponsor's product that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up

period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

All subjects with serious adverse events must be followed up for outcome.

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 30 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

- an overdose of Sponsor's product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
- an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

1. an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal.
2. an elevated AST or ALT lab value that is greater than or equal to 5X the upper limit of normal.

   *Note: For further guidance on the monitoring, treatment and follow-up of any ECI related to potential drug-induced liver injury (DILI), please see Section 12.8.

3. For the purpose of this dose-finding study, any suspected DLT occurring during dose escalation will be considered as medically important and reported as an ECI. If the event also meets the criteria for seriousness, follow the reporting guidelines for Serious Adverse Events (SAEs) outlined in Section 7.2.3.1

7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to the Sponsor as described in Section 7.2.3 - Immediate Reporting of Adverse Events to the Sponsor.

Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

The Sponsor will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the subjects in the trial. Any suspected endpoint which upon review is not progression of the cancer under study will be forwarded to global safety as a SAE within 24 hours of determination that the event is not progression of the cancer under study.

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

Table 10 Evaluating Adverse Events

An investigator who is a qualified physician, will evaluate all adverse events as to:

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Sponsor's product to be discontinued?	
Relationship to Sponsor's Product	Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Sponsor's Product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was the Sponsor's product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; or (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Sponsor's product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF REEXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).**	
Yes, there is a reasonable possibility of Sponsor's product relationship.	There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.	
No, there is not a reasonable possibility of Sponsor's product relationship	Subject did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a subject with overdose without an associated AE.)	

7.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to final database lock, changes made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to final database lock, will be documented in a supplemental SAP (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. Separate analysis plans (i.e., separate documents from the sSAP) will be developed to detail other planned analyses (i.e., those specific to the analysis of PK data, and future biomedical research

8.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in subsequent sections.

Study Design Overview	A Phase IB Dose Exploration Trial with MK-8628, a Small Molecule Inhibitor of the Bromodomain and Extra-Terminal (BET) Proteins, in Subjects with Selected Hematologic Malignancies
Treatment Assignment	This is an open label study with dose-level-specific cohorts.
Analysis Populations	Efficacy: Treatment Full Analysis Set (FAS), which is the same as ASaT Safety: DLT evaluable, and All Subjects as Treated (ASaT)
Primary Endpoint(s)	Proportion of subjects experiencing at least one DLT in cycle 1 (day 1 to 21)
Secondary Endpoints	Proportion of subjects in different response categories per protocol specified response criteria for each tumor type (AML or DLBCL)
Statistical Methods for Key Efficacy/Immunogenicity/ Pharmacokinetic Analyses	Proportion of subjects in different response categories will be estimated using Exact method based on binomial distribution (Clopper-Pearson Interval) for each tumor type.
Statistical Methods for Key Safety Analyses	Count and percentage of DLT will be provided. The Bayes credible interval (80%) for DLT rate will be estimated based on a prior distribution of Beta (1,1).
Interim Analyses	During the dose escalation phase, regular assessment of DLT from the most recent cohort will be performed.
Multiplicity	This is an estimated study and no multiplicity adjustment will be implemented
Sample Size and Power	The study is designed to assess the safety of MK-8628 in subjects with selected hematologic malignancies. The small numbers per cohort are not intended for statistical hypotheses. Up to 28 evaluable subjects (6-14 per two dose levels) will be included in each subject cohort (AML or DLBCL). This results in a study sample size of up to approximately 56 subjects. The final sample size will depend on the number of patients experiencing DLTs at each DL, and may be increased if additional DLTs are required.

8.2 Responsibility for Analyses/In-House Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the SPONSOR.

This trial is being conducted as an open-label study with dose level-specific cohorts.

8.3 Hypotheses/Estimation

Objectives of the study are stated in Section 3.0.

There are no statistical hypotheses for this study.

8.4 Analysis Endpoints

8.4.1 Safety Endpoints

The primary safety objective of this trial is to estimate proportion of subjects experiencing at least one DLT in cycle 1 (day 1 to 21) for each of the regimens and tumor type independently.

Other safety endpoints include incidence, severity and relationship of AEs, laboratory abnormalities, SAEs, discontinuations due to AEs, dose adaptations due to AEs

8.4.2 Efficacy/Pharmacokinetics/Pharmacodynamics Endpoints

Secondary efficacy endpoints are presented below:

Objective Response Rate (ORR): is defined as the percentage of subjects who have achieved confirmed complete response (CR) or partial response (PR) according to specified response criteria for each tumor type (AML or DLBCL) by the investigator review.

Duration of Response (DOR): is defined as the time interval between the date of the first confirmed response (CR/PR) (the response prior to confirmation) and the date of first documented disease progression based upon specified response criteria for each tumor type (AML or DLBCL) by the investigator review.

Disease Control Rate (DCR): is defined as the percentage of subjects who have achieved stable disease or confirmed complete response (CR) or confirmed partial response (PR) according to Response Evaluation Criteria in AML or DLBCL (see Section 7.1.2.7.1 and 7.1.2.7.2) by the investigator review. Subjects with missing response will be considered not to have achieved disease control.

Pharmacokinetics

Plasma parameters of MK-8628 as appropriate and according to analyses performed (non-compartmental or nonlinear mixed effect modelling).

Pharmacodynamics

Incidence and severity of AEs along with PK parameters will be analyzed in relation to the most pertinent biomarker(s), if any.

8.5 Analysis Populations

8.5.1 Safety Analysis Populations

DLT Evaluable population: subjects who receive at least 85% of the planned dose of study drug (18 days) or experience DLT during the first 21-day cycle.

The **All Subjects as Treated (ASaT)** population, also known as **treated population**, consisting of subjects who receive at least one dose of study drug, will be used for the analysis of all other safety data in this study.

8.5.2 Efficacy Analysis Populations

Treatment **Full Analysis Set** (**FAS**), also known as **evaluable for efficacy**: subjects who receive at least one dose of study drug

8.6 Statistical Methods

This section describes the statistical methods to address the primary and secondary objectives. Methods related to exploratory endpoints will be described in the supplemental SAP. Data will be presented by dose level and where appropriate by indication. No imputations for missing data will be made.

Pharmacokinetics and pharmacodynamics will be analyzed and reported separately.

8.6.1 Statistical Methods for Safety Analyses

Counts and percentage of DLT will be provided. Bayes credible interval (80%) for the DLT rate will be estimated based on a prior distribution of Beta (1,1) with other credible levels considered as clinically needed.

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences (AEs), laboratory tests, and vital signs. Counts and percentage of AE will be provided. Confidence intervals (95%, for rate of AE of clinical interest) will be estimated using an exact method based on binomial distribution (Clopper-Pearson interval).

8.6.2 Statistical Methods for Efficacy Analyses

ORR and DCR will be estimated using an exact method based on binomial distribution (Clopper-Pearson interval) for each tumor type (AML or DLBCL).

DOR will be estimated by Kaplan-Meier method.

8.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

The number and percentage of subjects screened, enrolled, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables, baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

8.7 Interim Analyses

During the dose escalation phase, regular assessment of data from the most recent cohort of subjects by cohort evaluable for DLT will be performed.

8.8 Multiplicity

This is an estimation study and no multiplicity adjustment will be implemented.

8.9 Sample Size and Power Calculations

The study is designed to assess the safety of MK-8628 in subjects with selected hematologic malignancies. The small numbers per cohort are not intended for statistical hypotheses.

Up to 28 evaluable subjects will be included in each subject cohort (AML or DLBCL). This results in a study sample size of up to approximately 56 subjects. There will be a maximum of 14 patients in each of the pre-specified dose levels for DLT evaluation. All AML subjects participating in the 20 mg BID regimen of the MK-8628-001 protocol (approximately up to 3 subjects) will count toward the initial 6 AML subjects needed for the 20 mg BID dose level in this study. The sample size (in AML 20mg BID cohort) of PN005 will be reduced according to the number of AML 20mg BID patients treated in PN001. PN005 will be analyzed on its' own but relevant results (limited to the AML 20mg BID cohort) in PN001 will be described in the clinical study report of PN005. And the DLT information for the AML 20mg BID cohort in PN001 will be used together with the AML 20mg BID cohort in PN005 for dose escalation/de-escalation decisions and RP2D decisions. The final sample size will depend on the number of patients experiencing DLTs at each dose level, and may be increased if additional dose levels are required. For ORR, the sample size will be dependent on the number of subjects in each cohort. Table 11 below provides Bayes credible interval and confidence interval with different number of events or responses for sample sizes of 6 and 14 to characterize the precision of the estimates for DLT rate and ORR, respectively.

Table 11 Bayes credible interval for DLT rate estimate and confidence interval for ORR estimate for different sample sizes and number of events

Sample Size	Number of Events or Responses	Observed Rate	80% Bayes credible interval	95% Bayes credible interval	95% confidence interval[a]
6	0	0	(0, 0.205)	(0, 0.348)	(0, 0.459)
6	1	0.167	(0.040, 0.391)	(0.013, 0.527)	(0.004, 0.641)
6	2	0.333	(0.146, 0.567)	(0.081, 0.685)	(0.043, 0.777)
6	3	0.500	(0.279, 0.721)	(0.184, 0.816)	(0.118, 0.882)
14	0	0	(0, 0.102)	(0, 0.181)	(0, 0.232)
14	1	0.071	(0.014, 0.194)	(0.004, 0.281)	(0.002, 0.339)
14	2	0.143	(0.053, 0.283)	(0.027, 0.373)	(0.018, 0.428)
14	3	0.214	(0.102, 0.367)	(0.062, 0.456)	(0.047, 0.508)
14	4	0.286	(0.156, 0.445)	(0.105, 0.533)	(0.084, 0.581)
14	5	0.357	(0.215, 0.519)	(0.154, 0.605)	(0.128, 0.649)
14	6	0.429	(0.276, 0.590)	(0.208, 0.672)	(0.177, 0.711)

[a.] Confidence intervals were calculated using Exact method based on binomial distribution (Clopper-Pearson interval).

8.10 Subgroup Analyses and Effect of Baseline Factors

Subgroup analyses and effect of baseline factors may be explored as appropriate.

8.11 Compliance (Medication Adherence)

Drug accountability data for trial treatment will be collected during the study. Any deviation from protocol-directed administration will be reported.

8.12 Extent of Exposure

Extent of Exposure for a subject is defined as number of cycles in which the subject receives the study medication. Summary statistics will be provided on Extent of Exposure for ASaT population.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by the Sponsor as summarized in Table 12.

Clinical supplies will be packaged to support enrollment and replacement subjects as required. When a replacement subject is required, the Sponsor or designee needs to be contacted prior to dosing the replacement supplies.

Table 12 Product Descriptions

Product Name & Potency	Dosage Form	Source/Additional Information
MK-8628 10 mg	Gelatin capsules (white, size 3)	Provided centrally by the Sponsor.
MK-8628 20 mg	Gelatin capsules (green, size 3)	Provided centrally by the Sponsor.

9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

Subjects will receive open label bottles. No kitting is required.

9.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded. Treatment (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

Section 5.8 outlines the criteria for allowing subjects who are discontinued from treatment to continue to be monitored in the trial.

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5 Discard/Destruction/Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial. For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

9.6 Standard Policies

Trial site personnel will have access to a central electronic treatment allocation/randomization system (IVRS/IWRS system) to allocate subjects, to assign

treatment to subjects and to manage the distribution of clinical supplies. Each person accessing the IVRS system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system, and they must not share their assigned PIN with anyone.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/ERC) or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules and regulations.

10.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

1. name, address, telephone number and e-mail address;
2. hospital or clinic address and telephone number;
3. curriculum vitae or other summary of qualifications and credentials; and
4. other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included

when reporting certain serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter trial, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

10.1.4 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this trial. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.2 Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is provided in Section 12.1 - Merck Code of Conduct for Clinical Trials.

The investigator also agrees to allow monitoring, audits, IRB/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the trial reimbursed to the investigator by the Sponsor.

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files.

ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this trial.

Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's trials. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in

conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different trial sites in that Member State, according to national regulations. For a single-center trial, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the trial report that summarizes the trial results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the trial [Clinical Study Report (CSR) CI]. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Merck, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAMA/FDAAA mandated trials. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAMA/FDAAA are that of the Sponsor and agrees not to submit any information about this trial or its results to the Clinical Trials Data Bank.

10.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

10.6 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her

electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

10.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC trials. For trials intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the trial results until the Sponsor notifies the investigator that all relevant regulatory authority decisions on the trial drug have been made with regard to pediatric-related regulatory filings. Merck will post a synopsis of trial results for approved products on www.clinicaltrials.gov by 12 months after the last subject's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

For multicenter trials, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicaltrials.gov if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual trial site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single trial site data prior to the main paper may be of value. Limitations of single trial site observations in a multicenter trial should always be described in such a manuscript.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that

contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

The Sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this trial 45 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

11.0 LIST OF REFERENCES

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12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of subject safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Such standards shall be endorsed for all clinical interventional investigations sponsored by Merck irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials which are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials which are not under the control of Merck.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine subject preferences, etc.

The design (i.e., subject population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research subjects must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

Merck selects investigative sites based on medical expertise, access to appropriate subjects, adequacy of facilities and staff, previous performance in Merck trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by Merck personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

B. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of trials it conducts. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing. In such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. Merck funding of a trial will be acknowledged in publications.

III. Subject Protection

A. IRB/ERC review

All clinical trials will be reviewed and approved by an independent IRB/ERC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/ERC prior to implementation, except that changes required urgently to protect subject safety and well-being may be enacted in anticipation of IRB/ERC approval. For each site, the IRB/ERC and Merck will approve the subject informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that subject welfare is of primary importance. Potential subjects will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care. Subjects are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Subjects are enrolled only after providing informed consent for participation. Subjects may withdraw from a Merck trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

Merck is committed to safeguarding subject confidentiality, to the greatest extent possible. Unless required by law, only the investigator, sponsor (or representative) and/or regulatory authorities will have access to confidential medical records that might identify the research subject by name.

D. Genomic Research

Genomic Research will only be conducted in accordance with informed consent and/or as specifically authorized by an Ethics Committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is Merck's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of Merck trials. Merck does not pay incentives to enroll subjects in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

Merck does not pay for subject referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible subjects.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by Merck, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local IRB/ERC may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, publications resulting from Merck trials will indicate Merck as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

V. Investigator Commitment

Investigators will be expected to review Merck's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens collected in this trial as outlined in Section 7.1.3.3 – Future Biomedical Research Sample Collection will be used to study various causes for how subjects may respond to a drug/vaccine. Future biomedical research specimen(s) will be stored to provide a resource for future trials conducted by the Sponsor focused on the study of biomarkers responsible for how a drug/vaccine enters and is removed by the body, how a drug/vaccine works, other pathways a drug/vaccine may interact with, or other aspects of disease. The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

All subjects enrolled in the clinical trial will be considered for enrollment in the Future Biomedical Research sub-trial.

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all subjects or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the subjects on Visit 1. If delayed, present consent at next possible Subject Visit. Informed consent must be obtained prior to collection of all Future Biomedical Research specimens. Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons.

A template of each trial site's approved informed consent will be stored in the Sponsor's clinical document repository. Each consent will be assessed for appropriate specimen permissions.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of subject consent for Future Biomedical Research will be captured in the electronic Case Report Forms (eCRFs). Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen Collections

Collection of specimens for Future Biomedical Research will be performed as outlined in the trial flow chart. In general, if additional blood specimens are being collected for Future Biomedical Research, these will usually be obtained at a time when the subject is having blood drawn for other trial purposes.

4. Confidential Subject Information for Future Biomedical Research

In order to optimize the research that can be conducted with Future Biomedical Research specimens, it is critical to link subject' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical trial data to the specimen. The clinical data allow specific analyses to be conducted. Knowing subject characteristics like gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for Future Biomedical Research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical trial site, unique codes will be placed on the Future Biomedical Research specimens for transfer to the storage facility. This first code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between subject identifiers and this first unique code will be held at the trial site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage

Specimens obtained for the Merck Biorepository will be used for analyses using good scientific practices. Analyses utilizing the Future Biomedical Research specimens may be performed by the Sponsor, or an additional third party (e.g., a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in this sub-trial. Future Biomedical Research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated

mailbox (clinical.specimen.management@merck.com) and a form will be provided to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. Documentation will be sent to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject's personal information and their specimens. In this situation, the request for specimen destruction can not be processed.

7. Retention of Specimens

Future Biomedical Research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the trial site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular trial, the trial site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated trial administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards (e.g., ISO17799) to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Subjects

No information obtained from exploratory laboratory studies will be reported to the subject, family, or physicians. Principle reasons not to inform or return results to the subject include: Lack of relevance to subject health, limitations of predictive capability, and concerns regarding misinterpretation.

If any exploratory results are definitively associated with clinical significance for subjects while the clinical trial is still ongoing, investigators will be contacted with information. After the clinical trial has completed, if any exploratory results are definitively associated with clinical significance, the Sponsor will endeavor to make such results available

through appropriate mechanisms (e.g., scientific publications and/or presentations). Subjects will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

Every effort will be made to recruit all subjects diagnosed and treated on Sponsor clinical trials for Future Biomedical Research.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the subject have been minimized. No additional risks to the subject have been identified as no additional specimens are being collected for Future Biomedical Research (i.e., only leftover samples are being retained).

The Sponsor has developed strict security, policies and procedures to address subject data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation there is risk that the information, like all medical information, may be misused.

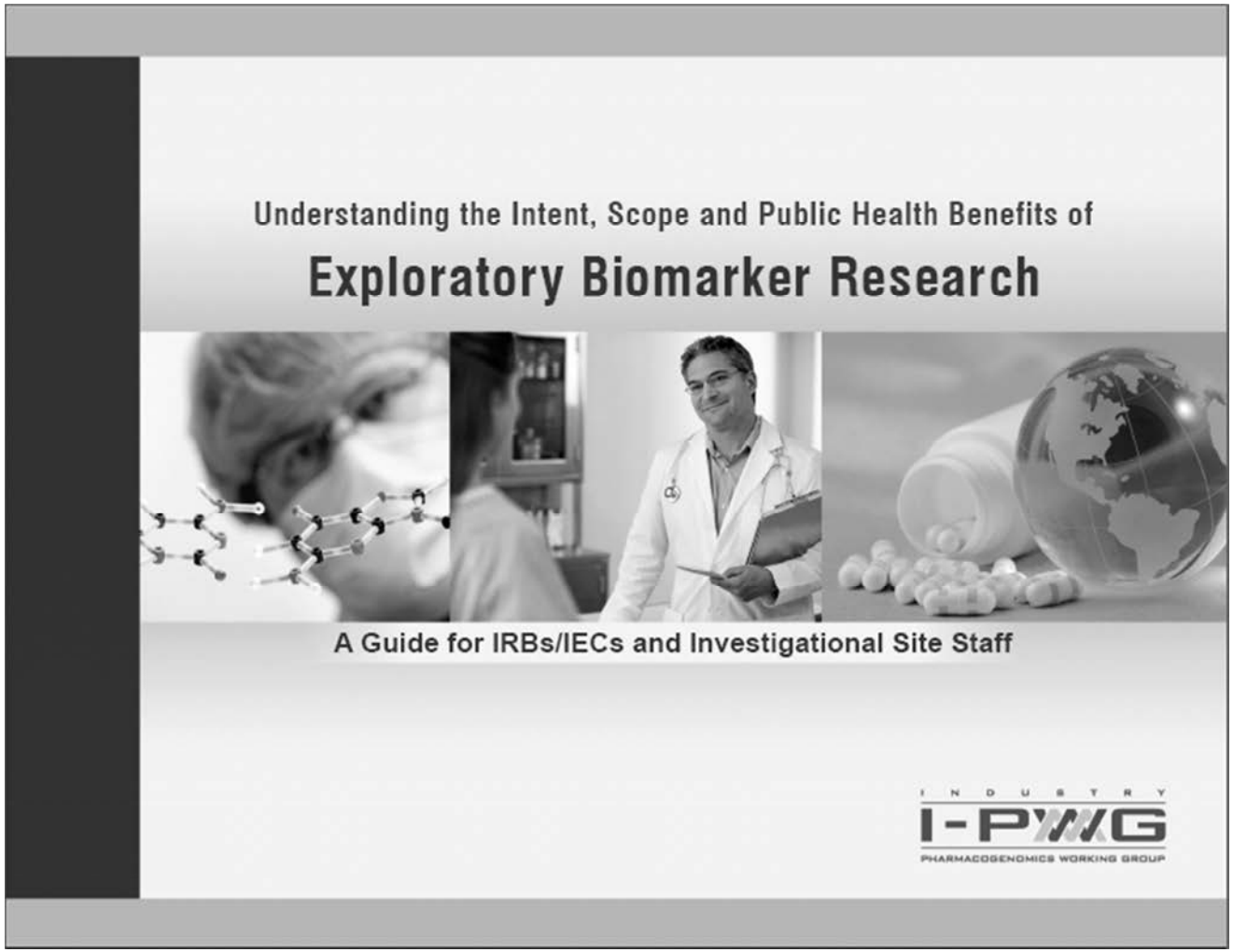
12. Questions

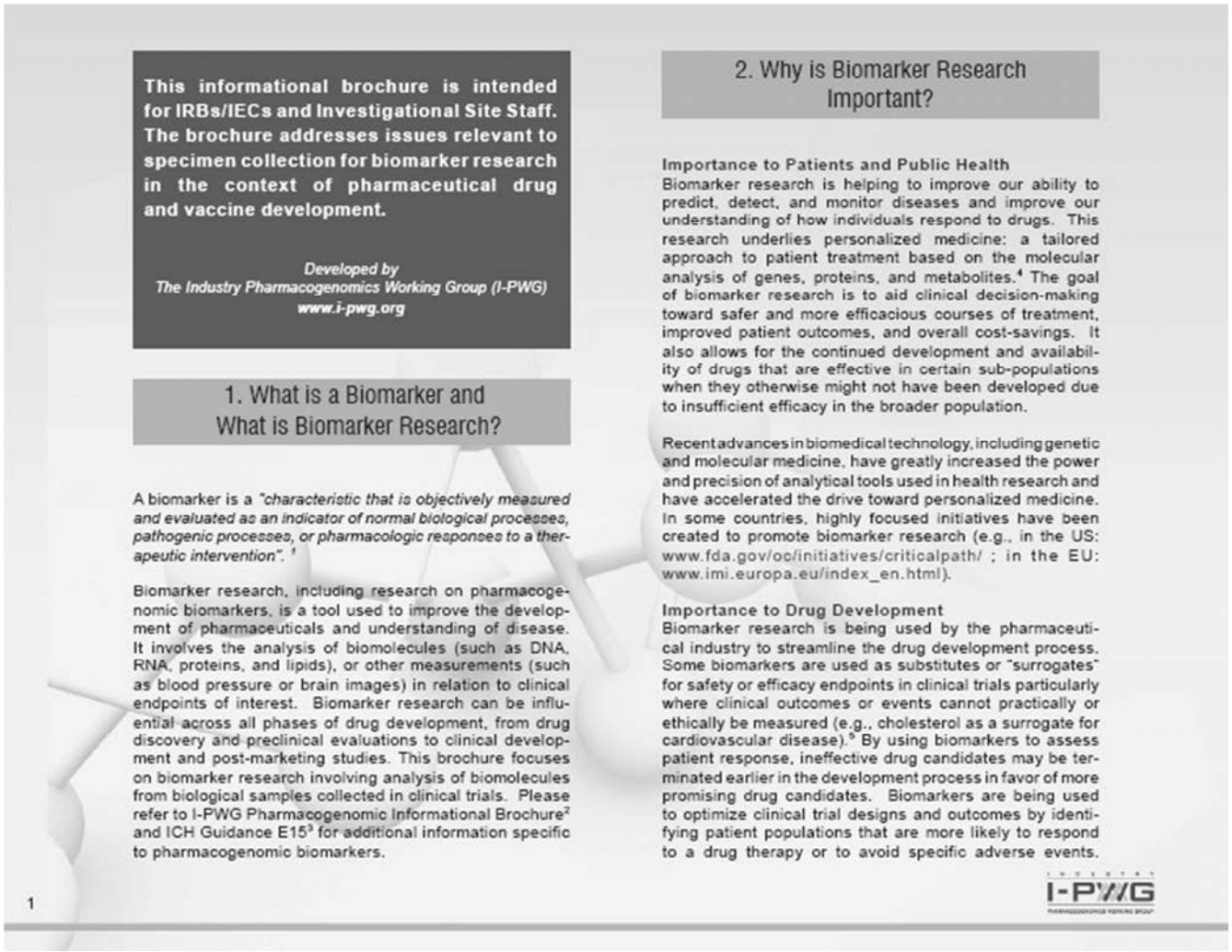
Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

13. References

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker
2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf

12.3 Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff





This informational brochure is intended for IRBs/IECs and Investigational Site Staff. The brochure addresses issues relevant to specimen collection for biomarker research in the context of pharmaceutical drug and vaccine development.

Developed by
The Industry Pharmacogenomics Working Group (I-PWG)
www.i-pwg.org

1. What is a Biomarker and What is Biomarker Research?

A biomarker is a *"characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention".* [1]

Biomarker research, including research on pharmacogenomic biomarkers, is a tool used to improve the development of pharmaceuticals and understanding of disease. It involves the analysis of biomolecules (such as DNA, RNA, proteins, and lipids), or other measurements (such as blood pressure or brain images) in relation to clinical endpoints of interest. Biomarker research can be influential across all phases of drug development, from drug discovery and preclinical evaluations to clinical development and post-marketing studies. This brochure focuses on biomarker research involving analysis of biomolecules from biological samples collected in clinical trials. Please refer to I-PWG Pharmacogenomic Informational Brochure[2] and ICH Guidance E15[3] for additional information specific to pharmacogenomic biomarkers.

2. Why is Biomarker Research Important?

Importance to Patients and Public Health
Biomarker research is helping to improve our ability to predict, detect, and monitor diseases and improve our understanding of how individuals respond to drugs. This research underlies personalized medicine: a tailored approach to patient treatment based on the molecular analysis of genes, proteins, and metabolites.[4] The goal of biomarker research is to aid clinical decision-making toward safer and more efficacious courses of treatment, improved patient outcomes, and overall cost-savings. It also allows for the continued development and availability of drugs that are effective in certain sub-populations when they otherwise might not have been developed due to insufficient efficacy in the broader population.

Recent advances in biomedical technology, including genetic and molecular medicine, have greatly increased the power and precision of analytical tools used in health research and have accelerated the drive toward personalized medicine. In some countries, highly focused initiatives have been created to promote biomarker research (e.g., in the US: www.fda.gov/oc/initiatives/criticalpath/ ; in the EU: www.imi.europa.eu/index_en.html).

Importance to Drug Development
Biomarker research is being used by the pharmaceutical industry to streamline the drug development process. Some biomarkers are used as substitutes or "surrogates" for safety or efficacy endpoints in clinical trials particularly where clinical outcomes or events cannot practically or ethically be measured (e.g., cholesterol as a surrogate for cardiovascular disease).[5] By using biomarkers to assess patient response, ineffective drug candidates may be terminated earlier in the development process in favor of more promising drug candidates. Biomarkers are being used to optimize clinical trial designs and outcomes by identifying patient populations that are more likely to respond to a drug therapy or to avoid specific adverse events.

I-PWG

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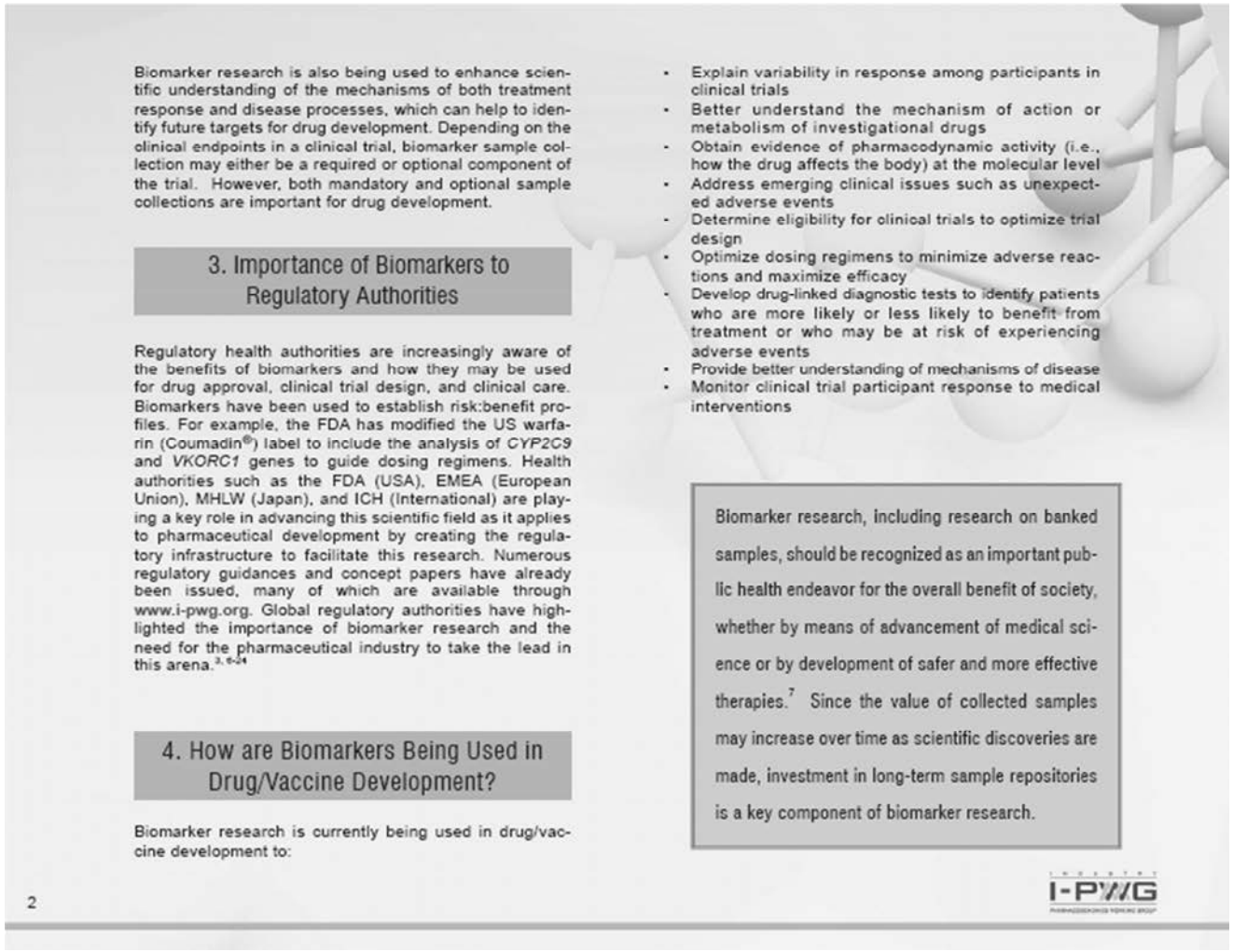
Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either be a required or optional component of the trial. However, both mandatory and optional sample collections are important for drug development.
3. Importance of Biomarkers to Regulatory Authorities
Regulatory health authorities are increasingly aware of the benefits of biomarkers and how they may be used for drug approval, clinical trial design, and clinical care. Biomarkers have been used to establish risk:benefit profiles. For example, the FDA has modified the US warfarin (Coumadin®) label to include the analysis of CYP2C9 and VKORC1 genes to guide dosing regimens. Health authorities such as the FDA (USA), EMEA (European Union), MHLW (Japan), and ICH (International) are playing a key role in advancing this scientific field as it applies to pharmaceutical development by creating the regulatory infrastructure to facilitate this research. Numerous regulatory guidances and concept papers have already been issued, many of which are available through www.i-pwg.org. Global regulatory authorities have highlighted the importance of biomarker research and the need for the pharmaceutical industry to take the lead in this arena.[3, 6-24]
4. How are Biomarkers Being Used in Drug/Vaccine Development?
Biomarker research is currently being used in drug/vaccine development to:
Explain variability in response among participants in clinical trials
Better understand the mechanism of action or metabolism of investigational drugs
Obtain evidence of pharmacodynamic activity (i.e., how the drug affects the body) at the molecular level
Address emerging clinical issues such as unexpected adverse events
Determine eligibility for clinical trials to optimize trial design
Optimize dosing regimens to minimize adverse reactions and maximize efficacy
Develop drug-linked diagnostic tests to identify patients who are more likely or less likely to benefit from treatment or who may be at risk of experiencing adverse events
Provide better understanding of mechanisms of disease
Monitor clinical trial participant response to medical interventions
Biomarker research, including research on banked samples, should be recognized as an important public health endeavor for the overall benefit of society, whether by means of advancement of medical science or by development of safer and more effective therapies.[7] Since the value of collected samples may increase over time as scientific discoveries are made, investment in long-term sample repositories is a key component of biomarker research.
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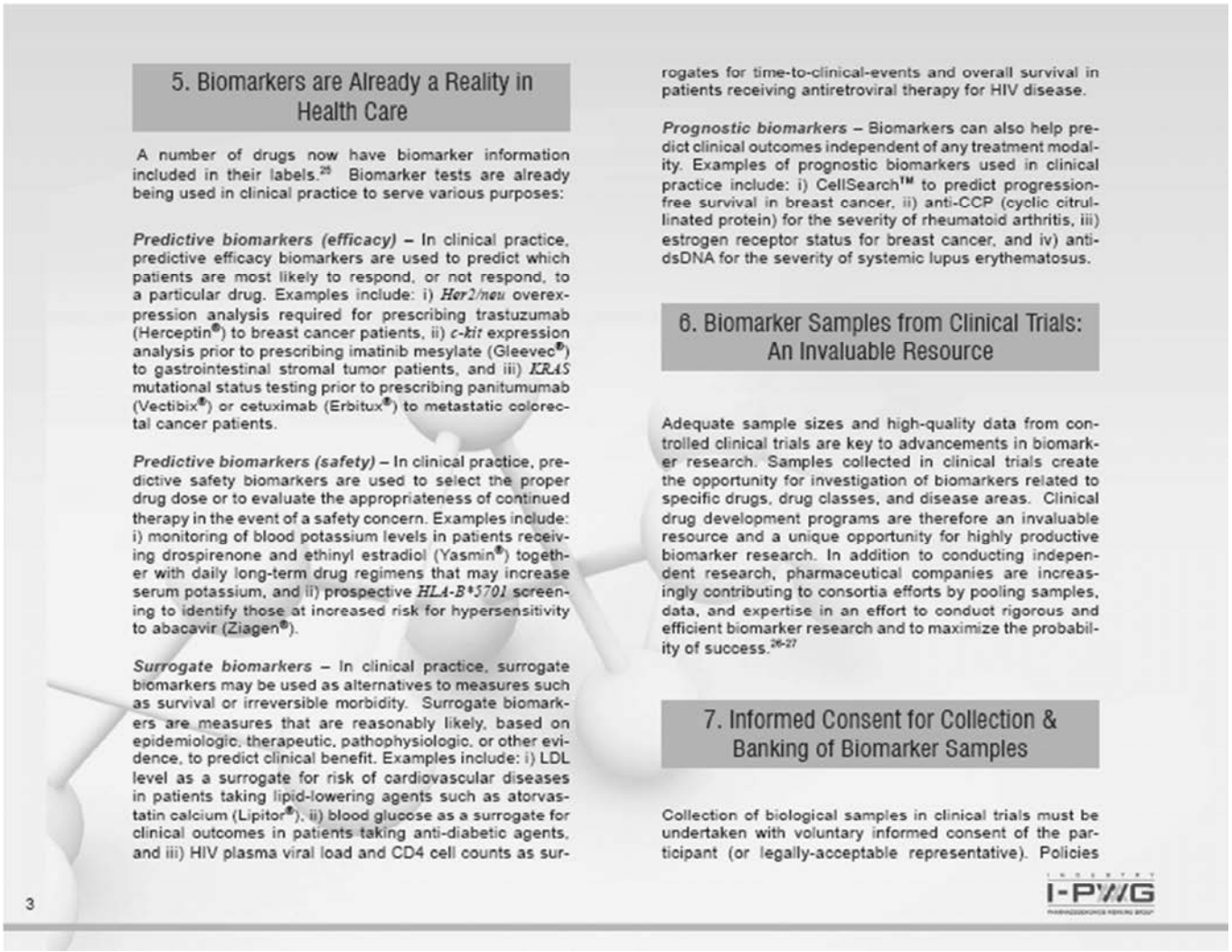

5. Biomarkers are Already a Reality in Health Care

A number of drugs now have biomarker information included in their labels.[25] Biomarker tests are already being used in clinical practice to serve various purposes:

Predictive biomarkers (efficacy) – In clinical practice, predictive efficacy biomarkers are used to predict which patients are most likely to respond, or not respond, to a particular drug. Examples include: i) *Her2/neu* overexpression analysis required for prescribing trastuzumab (Herceptin®) to breast cancer patients, ii) *c-kit* expression analysis prior to prescribing imatinib mesylate (Gleevec®) to gastrointestinal stromal tumor patients, and iii) *KRAS* mutational status testing prior to prescribing panitumumab (Vectibix®) or cetuximab (Erbitux®) to metastatic colorectal cancer patients.

Predictive biomarkers (safety) – In clinical practice, predictive safety biomarkers are used to select the proper drug dose or to evaluate the appropriateness of continued therapy in the event of a safety concern. Examples include: i) monitoring of blood potassium levels in patients receiving drospirenone and ethinyl estradiol (Yasmin®) together with daily long-term drug regimens that may increase serum potassium, and ii) prospective *HLA-B*5701* screening to identify those at increased risk for hypersensitivity to abacavir (Ziagen®).

Surrogate biomarkers – In clinical practice, surrogate biomarkers may be used as alternatives to measures such as survival or irreversible morbidity. Surrogate biomarkers are measures that are reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit. Examples include: i) LDL level as a surrogate for risk of cardiovascular diseases in patients taking lipid-lowering agents such as atorvastatin calcium (Lipitor®), ii) blood glucose as a surrogate for clinical outcomes in patients taking anti-diabetic agents, and iii) HIV plasma viral load and CD4 cell counts as surrogates for time-to-clinical-events and overall survival in patients receiving antiretroviral therapy for HIV disease.

Prognostic biomarkers – Biomarkers can also help predict clinical outcomes independent of any treatment modality. Examples of prognostic biomarkers used in clinical practice include: i) CellSearch™ to predict progression-free survival in breast cancer, ii) anti-CCP (cyclic citrullinated protein) for the severity of rheumatoid arthritis, iii) estrogen receptor status for breast cancer, and iv) anti-dsDNA for the severity of systemic lupus erythematosus.

6. Biomarker Samples from Clinical Trials: An Invaluable Resource

Adequate sample sizes and high-quality data from controlled clinical trials are key to advancements in biomarker research. Samples collected in clinical trials create the opportunity for investigation of biomarkers related to specific drugs, drug classes, and disease areas. Clinical drug development programs are therefore an invaluable resource and a unique opportunity for highly productive biomarker research. In addition to conducting independent research, pharmaceutical companies are increasingly contributing to consortia efforts by pooling samples, data, and expertise in an effort to conduct rigorous and efficient biomarker research and to maximize the probability of success.[26-27]

7. Informed Consent for Collection & Banking of Biomarker Samples

Collection of biological samples in clinical trials must be undertaken with voluntary informed consent of the participant (or legally-acceptable representative). Policies

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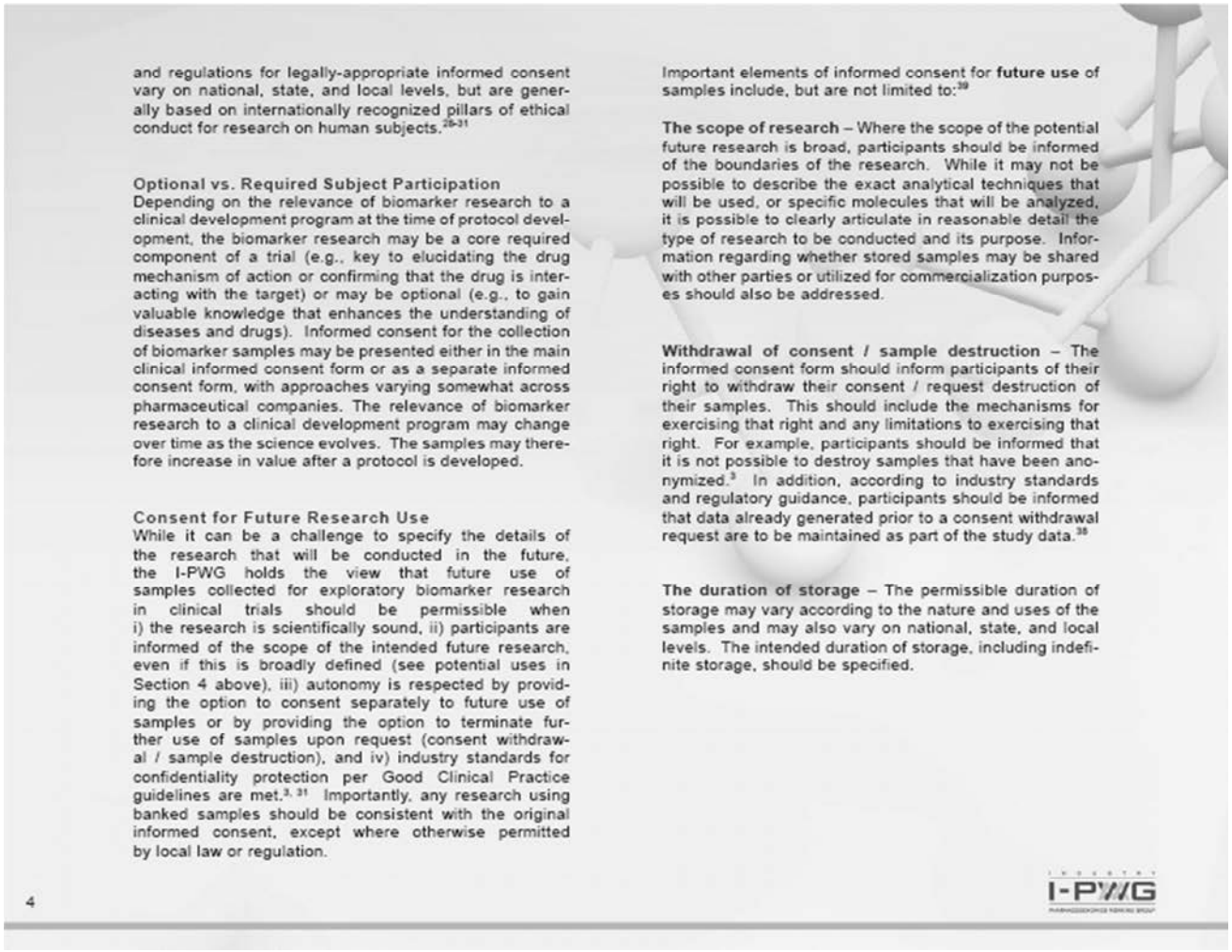

and regulations for legally-appropriate informed consent vary on national, state, and local levels, but are generally based on internationally recognized pillars of ethical conduct for research on human subjects.[28-31]

Optional vs. Required Subject Participation

Depending on the relevance of biomarker research to a clinical development program at the time of protocol development, the biomarker research may be a core required component of a trial (e.g., key to elucidating the drug mechanism of action or confirming that the drug is interacting with the target) or may be optional (e.g., to gain valuable knowledge that enhances the understanding of diseases and drugs). Informed consent for the collection of biomarker samples may be presented either in the main clinical informed consent form or as a separate informed consent form, with approaches varying somewhat across pharmaceutical companies. The relevance of biomarker research to a clinical development program may change over time as the science evolves. The samples may therefore increase in value after a protocol is developed.

Consent for Future Research Use

While it can be a challenge to specify the details of the research that will be conducted in the future, the I-PWG holds the view that future use of samples collected for exploratory biomarker research in clinical trials should be permissible when i) the research is scientifically sound, ii) participants are informed of the scope of the intended future research, even if this is broadly defined (see potential uses in Section 4 above), iii) autonomy is respected by providing the option to consent separately to future use of samples or by providing the option to terminate further use of samples upon request (consent withdrawal / sample destruction), and iv) industry standards for confidentiality protection per Good Clinical Practice guidelines are met.[3, 31] Importantly, any research using banked samples should be consistent with the original informed consent, except where otherwise permitted by local law or regulation.

Important elements of informed consent for **future use** of samples include, but are not limited to:[39]

The scope of research – Where the scope of the potential future research is broad, participants should be informed of the boundaries of the research. While it may not be possible to describe the exact analytical techniques that will be used, or specific molecules that will be analyzed, it is possible to clearly articulate in reasonable detail the type of research to be conducted and its purpose. Information regarding whether stored samples may be shared with other parties or utilized for commercialization purposes should also be addressed.

Withdrawal of consent / sample destruction – The informed consent form should inform participants of their right to withdraw their consent / request destruction of their samples. This should include the mechanisms for exercising that right and any limitations to exercising that right. For example, participants should be informed that it is not possible to destroy samples that have been anonymized.[3] In addition, according to industry standards and regulatory guidance, participants should be informed that data already generated prior to a consent withdrawal request are to be maintained as part of the study data.[38]

The duration of storage – The permissible duration of storage may vary according to the nature and uses of the samples and may also vary on national, state, and local levels. The intended duration of storage, including indefinite storage, should be specified.

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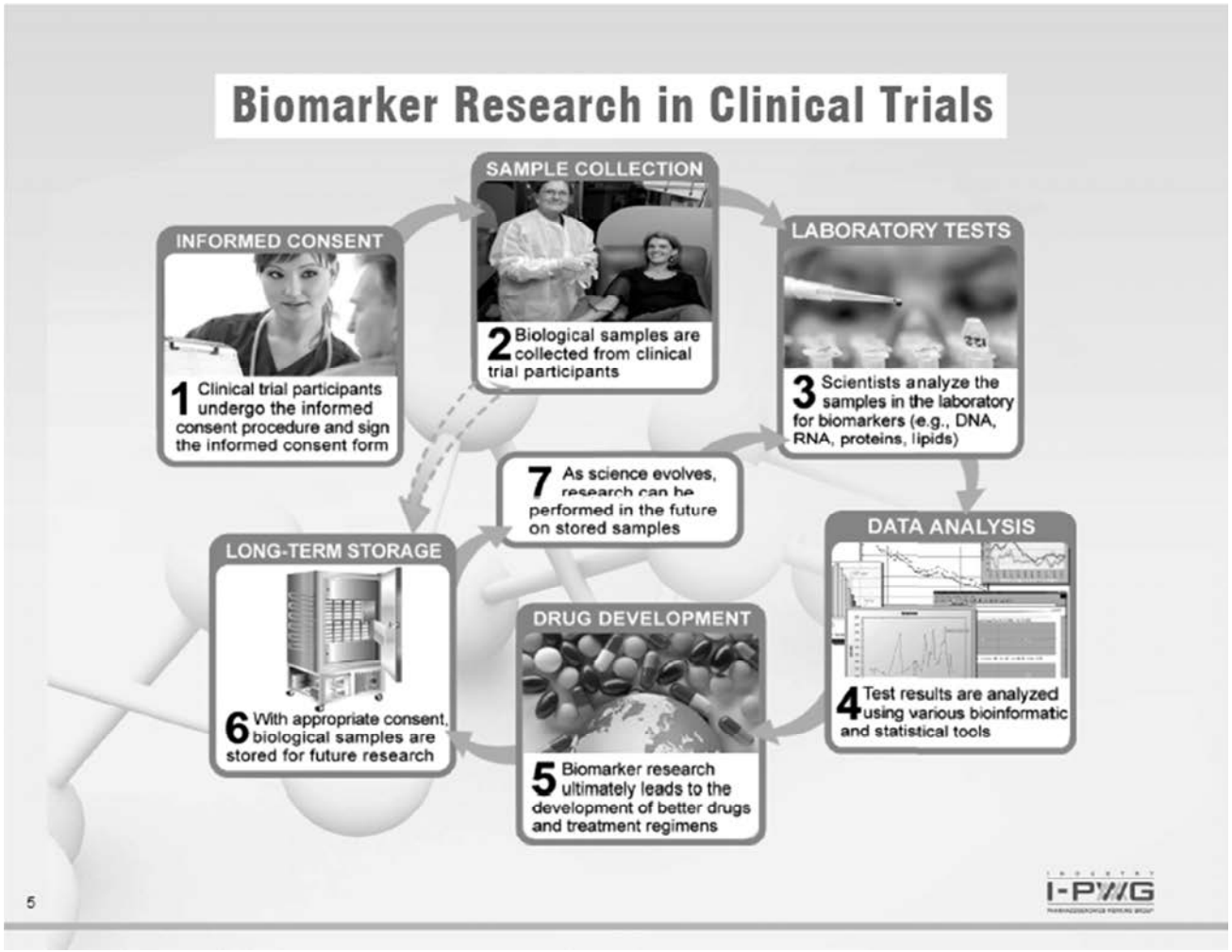
Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
INFORMED CONSENT
1 Clinical trial participants undergo the informed consent procedure and sign the informed consent form
LABORATORY TESTS
3 Scientists analyze the samples in the laboratory for biomarkers (e.g., DNA, RNA, proteins, lipids)
7 As science evolves, research can be performed in the future on stored samples
DATA ANALYSIS
4 Test results are analyzed using various bioinformatic and statistical tools
LONG-TERM STORAGE
6 With appropriate consent, biological samples are stored for future research
DRUG DEVELOPMENT
5 Biomarker research ultimately leads to the development of better drugs and treatment regimens
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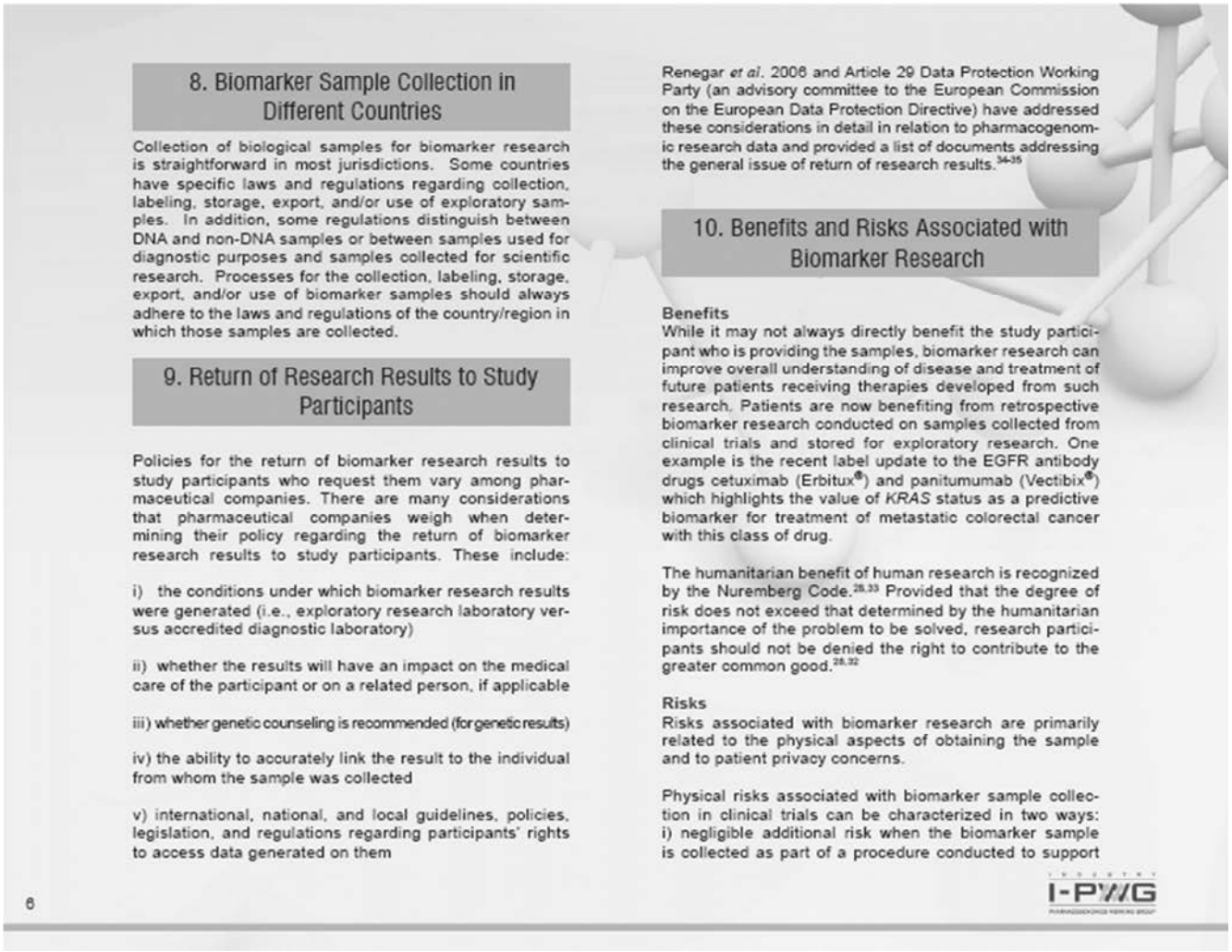

8. Biomarker Sample Collection in Different Countries

Collection of biological samples for biomarker research is straightforward in most jurisdictions. Some countries have specific laws and regulations regarding collection, labeling, storage, export, and/or use of exploratory samples. In addition, some regulations distinguish between DNA and non-DNA samples or between samples used for diagnostic purposes and samples collected for scientific research. Processes for the collection, labeling, storage, export, and/or use of biomarker samples should always adhere to the laws and regulations of the country/region in which those samples are collected.

9. Return of Research Results to Study Participants

Policies for the return of biomarker research results to study participants who request them vary among pharmaceutical companies. There are many considerations that pharmaceutical companies weigh when determining their policy regarding the return of biomarker research results to study participants. These include:

i) the conditions under which biomarker research results were generated (i.e., exploratory research laboratory versus accredited diagnostic laboratory)

ii) whether the results will have an impact on the medical care of the participant or on a related person, if applicable

iii) whether genetic counseling is recommended (for genetic results)

iv) the ability to accurately link the result to the individual from whom the sample was collected

v) international, national, and local guidelines, policies, legislation, and regulations regarding participants' rights to access data generated on them

Renegar *et al*. 2008 and Article 29 Data Protection Working Party (an advisory committee to the European Commission on the European Data Protection Directive) have addressed these considerations in detail in relation to pharmacogenomic research data and provided a list of documents addressing the general issue of return of research results.[34-35]

10. Benefits and Risks Associated with Biomarker Research

Benefits

While it may not always directly benefit the study participant who is providing the samples, biomarker research can improve overall understanding of disease and treatment of future patients receiving therapies developed from such research. Patients are now benefiting from retrospective biomarker research conducted on samples collected from clinical trials and stored for exploratory research. One example is the recent label update to the EGFR antibody drugs cetuximab (Erbitux®) and panitumumab (Vectibix®) which highlights the value of *KRAS* status as a predictive biomarker for treatment of metastatic colorectal cancer with this class of drug.

The humanitarian benefit of human research is recognized by the Nuremberg Code.[28,33] Provided that the degree of risk does not exceed that determined by the humanitarian importance of the problem to be solved, research participants should not be denied the right to contribute to the greater common good.[28,32]

Risks

Risks associated with biomarker research are primarily related to the physical aspects of obtaining the sample and to patient privacy concerns.

Physical risks associated with biomarker sample collection in clinical trials can be characterized in two ways: i) negligible additional risk when the biomarker sample is collected as part of a procedure conducted to support

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other core trial objectives, and ii) some added risk where the sampling procedure would otherwise have not been performed as a core component of a trial. Risks are also determined by the invasiveness of the sample collection procedure.

Privacy risks are generally those associated with the inappropriate disclosure and misuse of data. Pharmaceutical companies have policies and procedures for confidentiality protection to minimize this risk for all data collected and generated in clinical trials. These may vary across companies, but are based on industry standards of confidentiality and privacy protection highlighted in the following section. Importantly, privacy risks inherent to biomarker data are no greater than other data collected in a clinical trial.

11. Privacy, Confidentiality, and Patient Rights

Maintaining the privacy of study participants and the confidentiality of information relating to them is of paramount concern to industry researchers, regulators, and patients. Good Clinical Practice (GCP), the standard adhered to in pharmaceutical clinical research, is a standard that

"...provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected",

where confidentiality is defined as, *"The prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity."*

This standard dictates that *"the confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements."* [31]

Exploratory biomarker research in pharmaceutical development is commonly conducted in research laboratories that are not accredited to perform diagnostic tests used for healthcare decision-making. Therefore, results from exploratory biomarker research usually are not appropriate for use in making decisions about a trial participant's health. In addition, exploratory research data should not be included as part of a participant's medical record accessible for use by insurance companies. Legislation and policies to protect individuals against discrimination based on genetic information continually evolve based on social, ethical, and legal considerations. Examples of such legislation include the Human Tissue Act 2004 (UK) and the Genetic Information Nondiscrimination Act (GINA) 2008 (USA).[35-37]

12.Where to Get More Information?

Educational resources related to biomarker and pharmacogenomic research that caters to health care professionals, IRBs/IECs, scientists, and patients are continually being created and are publicly available. Links to many of these resources are available through the I-PWG website: www.i-pwg.org.

13. What is I-PWG?

The Industry Pharmacogenomics Working Group (I-PWG) (formerly the Pharmacogenetics Working Group) is a voluntary association of pharmaceutical companies engaged in pharmacogenomic research. The Group's activities focus on non-competitive educational, informational, ethical, legal, and regulatory topics. The Group provides information and expert opinions on these topics and sponsors educational/informational programs to promote better understanding of pharmacogenomic and other biomarker research for key stakeholders. The I-PWG interacts with regulatory author-

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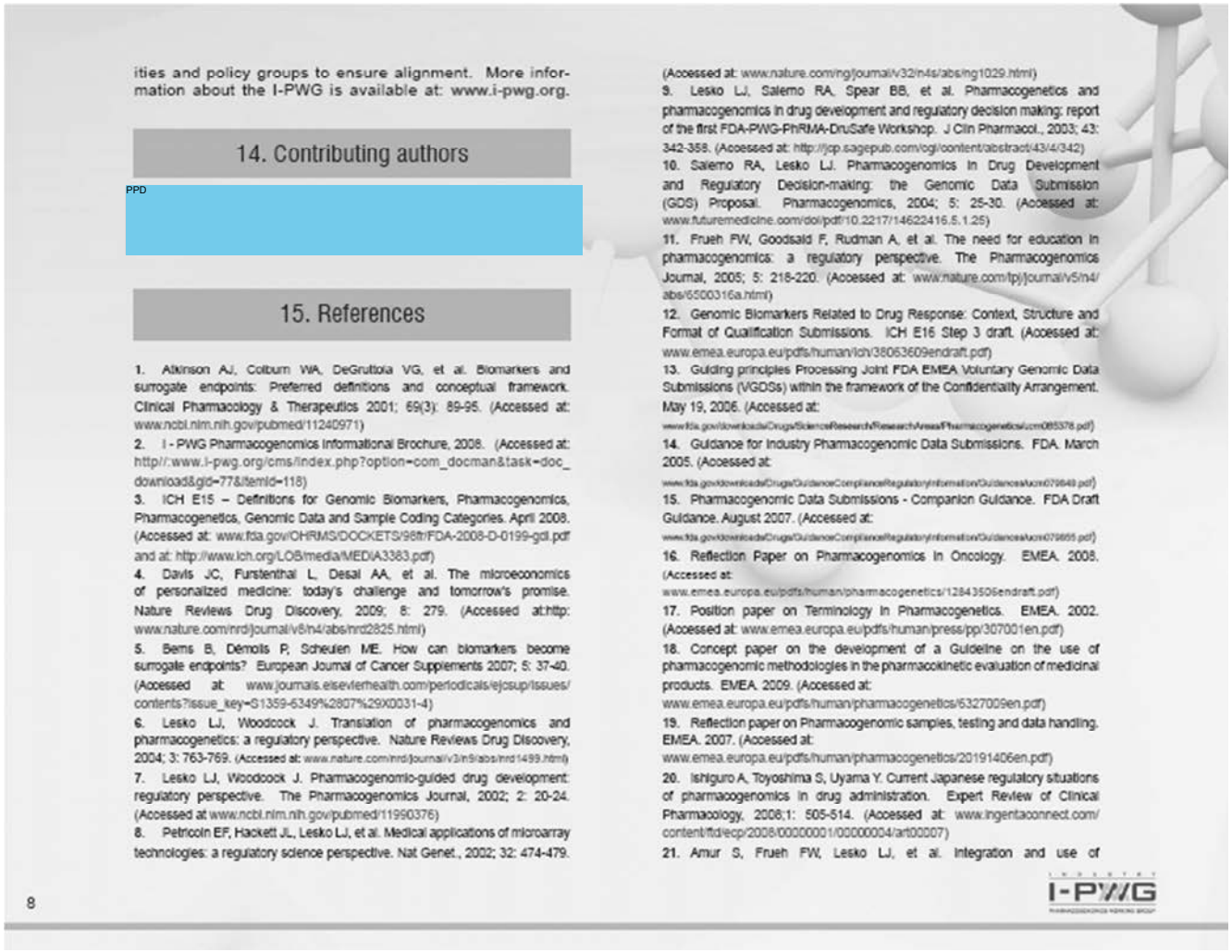

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

14. Contributing authors

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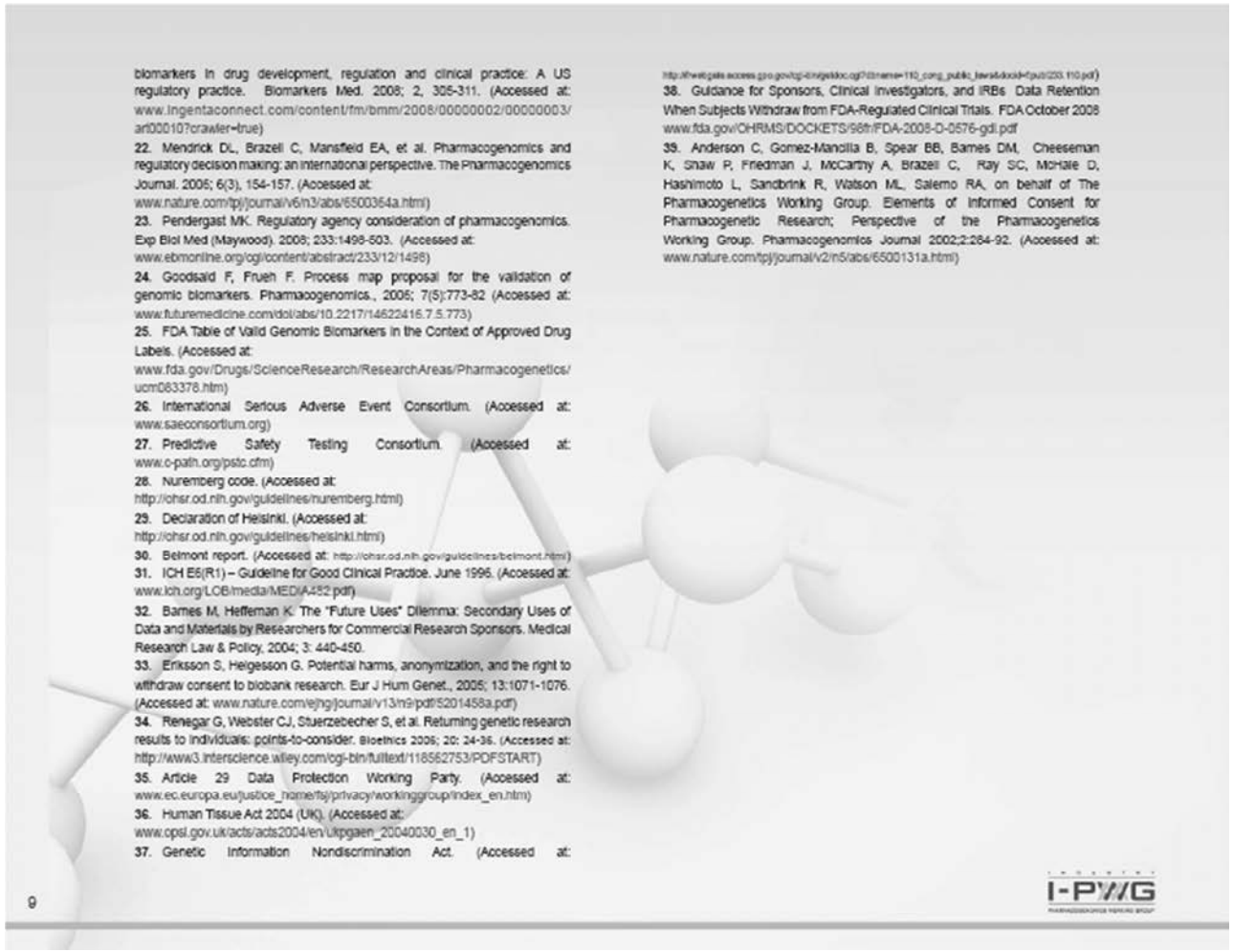

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12.4 Response Assessment of AML

Table 13 Response Assessment of AML [45]

Category	Definition
Complete remission (CR)*	Bone marrow blasts < 5%; absence of blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count > 1.0×10^9/L (1000/μL); platelet count > 100×10^9/L (100 000/μL); independence of red cell transfusions
CR with incomplete recovery (CRi)†	All CR criteria except for residual neutropenia (< 1.0×10^9/L [1000/μL]) or thrombocytopenia (< 100×10^9/L [100 000/μL])
Morphologic leukemia-free state‡	Bone marrow blasts < 5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required
Partial remission (PR)	Relevant in the setting of phase 1 and 2 clinical trials only; all hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pretreatment bone marrow blast percentage by at least 50%
Cytogenetic CR (CRc)§	Reversion to a normal karyotype at the time of morphologic CR (or CRi) in cases with an abnormal karyotype at the time of diagnosis; based on the evaluation of 20 metaphase cells from bone marrow
Molecular CR (CRm)‖	No standard definition; depends on molecular target
Treatment failure	
Resistant disease (RD)	Failure to achieve CR or CRi (general practice; phase 2/3 trials), or failure to achieve CR, CRi, or PR (phase 1 trials); only includes patients surviving ≥ 7 days following completion of initial treatment, with evidence of persistent leukemia by blood and/or bone marrow examination
Death in aplasia	Deaths occurring ≥ 7 days following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 days of death, without evidence of persistent leukemia
Death from indeterminate cause	Deaths occurring before completion of therapy, or < 7 days following its completion; or deaths occurring ≥ 7 days following completion of initial therapy with no blasts in the blood, but no bone marrow examination available
Relapse¶	Bone marrow blasts ≥ 5%; or reappearance of blasts in the blood; or development of extramedullary disease

* All criteria need to be fulfilled; marrow evaluation should be based on a count of 200 nucleated cells in an aspirate with spicules; if ambiguous, consider repeat exam after 5 to 7 days; flow cytometric evaluation may help to distinguish between persistent leukemia and regenerating normal marrow; a marrow biopsy should be performed in cases of dry tap, or if no spicules are obtained; no minimum duration of response required.

† The criterion of CRi is of value in protocols using intensified induction or double induction strategies, in which hematologic recovery is not awaited, but intensive therapy will be continued. In such protocols, CR may even not be achieved in the course of the entire treatment plan. In these instances, the overall remission rate should include CR and CRi patients. Some patients may not achieve complete hematologic recovery upon longer observation times.

‡ This category may be useful in the clinical development of novel agents within phase 1 clinical trials, in which a transient morphologic leukemia-free state may be achieved at the time of early response assessment.

¶ In cases with low blast percentages (5-10%), a repeat marrow should be performed to confirm relapse. Appearance of new dysplastic changes should be closely monitored for emerging relapse. In a patient who has been recently treated, dysplasia or a transient increase in blasts may reflect a chemotherapy effect and recovery of hematopoiesis. Cytogenetics should be tested to distinguish true relapse from therapy-related MDS/AML.

12.5 Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: the Lugano Classification

Table 14 Response Assessment of Hodgkin and Non Hodgkin Lymphoma: the Lugano Classification [46]

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

Response and Site	PET-CT Based Response	CT-Based Response
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

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

12.6 ECOG Performance Status

ECOG	Characteristics
0	Normal activity
1	Symptoms of disease, but ambulatory and able to carry out activities of daily living
2	Out of bed more than 50% of the time, occasionally needs assistance
3	In bed more than 50% of the time, needs nursing care
4	Bed ridden, may need hospitalization

12.7 Calculation of Renal Clearance

Subjects aged < 65 years: **Cockroft &Gault** formula

Male = 1.25 x **weight (kg)** x (140-**age**) / serum **creatinine (µmol/L)**

Female = 1.04 x **weight (kg)** x (140-**age**) / serum **creatinine (µmol/L)**

Subjects aged ≥65 years: **MDRD** (Modification of Diet in Renal Disease) formula

Male = 186 x (serum **creatinine (µmol/L)** x 0,0113)$^{-1,154}$ x **age**$^{-0,203}$

x 1,21 in subjects with black skin

x 0.742 in female

Clearance can be calculated using tools available via the internet, e.g.

http://filfola.fr/medecine/cockroft_MDRD.html

or

http://mdrd.com

12.8 Guidance for Potential Drug-Induced Liver Injury (DILI)

12.8.1 Purpose

The purpose of this document is to provide guidance to enable the investigator/study coordinator to provide clinical follow-up and systematically gather and report data on potential DILI. The data collected will be used by the Sponsor to create narratives for regulatory agency reporting.

12.8.2 Introduction

Hepatotoxicity is injury or damage to the liver that may be associated with impaired liver function (Navarro and Senior 2006). Drug-induced hepatotoxicity is one of the most common causes of termination of drug development, a major reason for refusal of market authorization and for restricted use, and the single most important cause of the withdrawal of market authorization for products (Björnsson 2006). Thus, drug-induced hepatotoxicity is a major concern during the discovery, development to post-authorization phases of the product life cycle (excerpted from Draft Guidance Document, Hepatotoxicity of Health Products, Ministry of Public Health, Canada, December 2010).

As stated in the United States Food and Drug Administration (FDA) "Guidance for Industry - Drug-Induced Liver Injury: Premarketing Clinical Evaluation"; hepatocellular injury (usually detected by serum aminotransferase elevations [AT]) can be caused by drugs that rarely, if ever, cause severe DILI (e.g., aspirin, tacrine, statins, and heparin), as well as by drugs that do cause such injury. The frequency of serum AT elevations also is not a good indicator of a potential for severe DILI because drugs such as tacrine (not a cause of severe DILI) can cause AT elevations in as many as 50 percent of subjects. Very high levels of observed ATs may be a somewhat better indicator of potential for severe DILI, but the most specific indicator is evidence of altered liver function accompanying or promptly following evidence of hepatocellular injury.

The single clearest (most specific) predictor found to date of a drug's potential for severe hepatotoxicity, is the occurrence of hepatocellular injury (AT elevation) accompanied by increased serum total bilirubin (TBL) not explained by any other cause, such as viral hepatitis or exposure to other hepatotoxins, and without evidence of cholestasis, together with an increased incidence of AT elevations in the overall trial population compared to control. Increased plasma prothrombin time, or its international normalized ratio (INR), a consequence of reduced hepatic production of Vitamin K-dependent clotting factors, is another potentially useful measure of liver function that might suggest the potential for severe liver injury.

Recognition of the importance of altered liver function, in addition to liver injury, began with Hyman Zimmerman's observation that drug-induced hepatocellular injury (i.e., AT elevation) accompanied by jaundice (i.e., TBL elevation) had a poor prognosis, with a 10 to 50 percent mortality from acute liver failure (in pretransplantation days) (Zimmerman 1978, 1999). This became known as "Hy's Law". This document describes the recommended process for monitoring and evaluation of subjects meeting the laboratory criteria for potential DILI defined as:

- an elevated alanine transaminase (ALT) or aspartate transaminase (AST) lab value that is greater than or equal to three times (3X) the upper limit of normal (ULN) and
- an elevated TBL lab value that is greater than or equal to two times (2X) ULN and
- at the same time, an alkaline phosphatase (ALP) lab value that is less than 2X ULN,

as a result of within-protocol-specific testing or unscheduled testing.

The protocol identifies these laboratory criteria for potential DILI as ECIs. ECIs are selected adverse experiences that must be reported to the Sponsor within 24 hours. The Principal Investigator should record these ECIs on the Adverse Experience Case Report Forms (CRFs) and complete pertinent adverse experience fields as outlined in the Data Entry Guidelines (DEGs).

12.8.3 Close Observation Recommendations

The following steps should be taken when a subject is observed to have an elevated AST or ALT lab value that is greater than or equal to 3X ULN and an elevated TBL lab value that is greater than or equal to 2X ULN and, at the same time, an ALP lab value that is less than 2X ULN, as a result of within-protocol-specific testing or unscheduled testing. In addition, close monitoring of *isolated* bilirubin increases greater than 2X ULN will be required.

Initiate **close observation,** defined below, and continue performing **follow-up to resolution.**

Close observation is defined as follows:

- Repeat liver enzyme and serum bilirubin tests two (2) or three (3) times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or study drug has been discontinued and the subject is asymptomatic.
    - For subjects with *isolated* bilirubin elevations greater than 2X ULN, repeat serum bilirubin tests every 2 weeks until the bilirubin returns to normal or baseline.
- Obtain a more detailed history of symptoms and prior or concurrent diseases (see 12.8.5).
- Obtain a history of concomitant medication use (including prescription and nonprescription medications, herbal and other dietary supplements), alcohol use, recreational drug use and special diets (see Section 12.8.5 for details).
- Obtain a history of exposure to chemical agents or other environmental toxins.

- Obtain additional history and complete Stage 1 work-up to attempt to rule out other potential causes of the transaminase elevation, including but not limited to the following: acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; non-alcoholic steatohepatitis (NASH); hypoxic/ischemic hepatopathy; and biliary tract disease (see Section 12.8.5 for details).
- Consider gastroenterology or hepatology consultation.

In general, treatment with study therapy should be stopped if the laboratory criteria for potential DILI are met. Please refer to the specific discontinuation criteria in the protocol as appropriate.

12.8.4 Hepatic Assessment Flow Chart

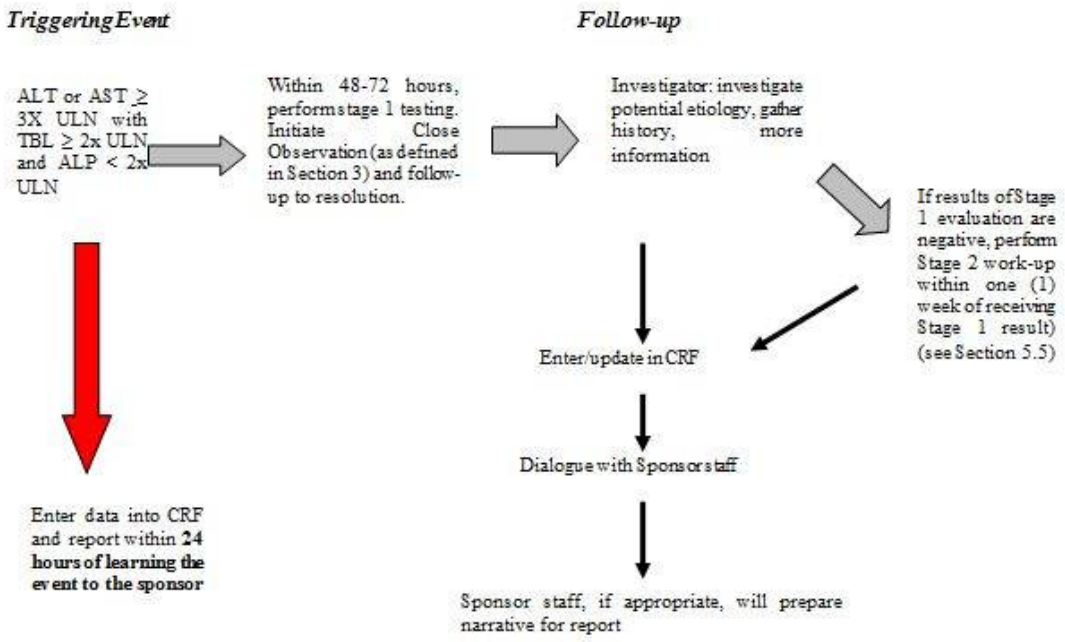

Figure 4 Hepatic Assessment Flow Chart

Factors to Consider in Assessing Potential DILI

When there is a potential DILI, it is important to thoroughly assess the subject's history, hepatic risk factors, clinical condition and hepatic function until resolution (normal or baseline levels).

Answers to the following questions should be recorded in source documents and in appropriate CRFs as outlined in the DEGs.

12.8.4.1 Study Medication

Considerations should include the following: What was the time interval between administration of study medication and the laboratory abnormality(ies)? What is the status of study medication use: Continuing? Interrupted? Discontinued? Was the subject re-challenged with study medication?

12.8.4.2 Treatment

Record any concomitant treatments.

12.8.4.3 Signs and Symptoms (associated with the potential DILI event)

Does the subject have a concomitant illness? Does the subject currently exhibit signs or symptoms of hepatitis/DILI? What are the subject's signs and symptoms (see examples below)? What are the pertinent findings from medical history, physical/laboratory examination (e.g., fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia > 5%, hepatomegaly, splenomegaly, etc.) that could suggest DILI?

Category	Examples of Signs and Symptoms
Blood/lymphatic	Eosinophilia, coagulopathy, susceptibility to bleeding/bruising
Circulatory	Varicose veins, edema
Constitutional	Fever, fatigue, malaise, weight gain, other (identify).
Digestive/hepatic	Anorexia, diarrhea, bloody or black stool, light-colored stools, nausea, vomiting, hematemesis, upper quadrant abdominal pain, upper quadrant tenderness, hepatomegaly, jaundice, splenomegaly, ascites, cholestasis
Endocrine/reproductive	Loss of libido
Integumentary	Rash, pruritus
Muscular	Myalgia
Nervous	Changes in mental status or level of consciousness
Urinary	Dark urine

12.8.4.4 Confounding Variables

What are the relevant medical history and findings? What is the differential diagnosis? What risk factors does the subject have for hepatic injury? (See examples below.) Provide onset of risk factor and duration.

Category	Examples of Confounding Variables
Subject medical history	Autoimmune disorder, cancer, Gilbert's syndrome, obesity, Wilson's disease
Substance use/abuse	Alcohol, illegal drugs, illegal intravenous (IV) drugs
Prior & Concomitant Medications: Review all non-study medications and therapies, including: over-the-counter (OTC), as well as prescription. Ask the subject to bring products/packaging to site and review contents.	History of recent concomitant acetaminophen (APAP)/paracetamol use, excessive nonsteroidal anti-inflammatory drug (NSAID) intake, use of non-study drug or therapy that can cause liver damage or idiosyncratic adverse drug reactions
Herbal and nutritional supplements	Herbal, complementary therapies, and nutritional supplements
Adulteration of products	History of previous exposure to the product or a similar product, and information on potential contamination or adulteration of products
Chemical exposure	Occupational or in other situations
Potential exposure to infectious agents	Infectious hepatitis, transfusion, travel, tattoos, sexually transmitted diseases, new sexual partner, shared needles
Special Diet	Special diet started since randomization
Other	Recent physical trauma, excessive exercise, or other prolonged physical exertion
Family history	Autoimmune disorder, cancer, Gilbert's syndrome, Wilson's disease

12.8.4.5 Evaluation Algorithm for Potential DILI if there are No Other Clinical Reasons

Note: If clear etiology for the laboratory abnormalities has been confirmed, Stage 1 and 2 testing may not be required. In this case, consultation with the Sponsor is recommended.

Stage 1 work-up should be performed within 48-72 hours:

- ALT
- AST
- Bilirubin: total, direct, indirect
- Alkaline phosphatase (ALP)
- Prothrombin Time (PT)/international normalized ratio (INR)
- Creatine phosphokinase (CPK)
- Manual eosinophil count (if automated count was elevated)
- Toxicology screen for drugs of abuse (including ethanol) and for acetaminophen/paracetamol level should also be sent. Investigators may order additional toxicology tests as clinically indicated.
- Evaluate subject for the following signs and symptoms: fatigue, nausea, vomiting, right upper quadrant abdominal pain or tenderness, fever, rash.
- Obtain the following additional history and assessment for associated risk/confounding factors:
    - More detailed history of symptoms and prior or concurrent illness
    - Aminotransferase values obtained prior to the study or administration of study medication
    - Alcohol consumption (recent and historical)
    - Acetaminophen (APAP)/paracetamol use
    - New prescription, concomitant, or non-prescription (including herbal and other dietary supplements) medications
    - Unusual foods (e.g. mushrooms) or special diets. Consumption of seasonal foods.
    - Recreational drug use
    - Prior history of liver injury or disease, including but not limited to Gilbert's syndrome, autoimmune disorders, cancer, Wilson's disease, NASH, alcoholic or infectious hepatitis, biliary tract disease, hypoxic/ischaemic hepatopathy
    - Obesity/abdominal adiposity (record weight, height, and waist circumference)
    - Occupational history and history of exposure to chemical agents or other environmental toxins
    - Recent travel (last three [3] years)

- Transfusion history

- Perform the following required laboratory tests**:**
  - Albumin
  - Eosinophils (percentage and absolute; obtain manual count if automated count is elevated)
  - Viral hepatitis serologies (obtain appropriate consent prior to testing, if required locally)
    - A (IgG, IgM)
    - B (HepBs Ag, Hep Bs Ab, Hep Bc Ab, Hep Be Ag)
    - C (RNA)
    - D (requires concomitant hepatitis B infection)
  - Human Immunodeficiency Virus (HIV) testing (obtain appropriate consent prior to testing, if required locally)
  - Evaluation for autoimmune hepatitis:
    - Serum gamma globulin levels/ serum protein electrophoresis
    - Antinuclear antibody (ANA)
    - Anti-mitochondrial antibody (if ALP or TBL >ULN)
  - If AST/ALT ratio is greater than one (1) with suspicions of increased alcohol intake, perform the following:
    - Gamma-glutamyl transferase (GGT)
- Obtain a right upper quadrant ultrasound

Stage 2 work-up tests should be drawn within one (1) week of receiving the Stage 1 work-up results and the results of Stage 1 evaluation are negative.

Note: A specific test may be performed earlier if the investigator determines that the clinical presentation leads to a certain diagnosis.

Stage 2 work-up:

- Perform the following laboratory tests:
  - Genetic test for Gilbert's disease if there is a suspicious history. Ensure appropriate subject consent is obtained for this test.
  - Viral hepatitis E (IgG and IgM, obtain appropriate consent prior to testing, if required locally)
  - Anti-smooth muscle antibody
  - Anti-liver-kidney microsomal antibody
  - Anti-soluble liver antigen

- Serologies for the following:
  - Cytomegalovirus (CMV) (IgG, IgM)
  - Epstein-Barr Virus (EBV) (IgG, IgM)
  - Herpes simplex
  - Toxoplasmosis
  - Varicella
  - Parvovirus
- Ceruloplasmin
- Serum alpha-1 anti trypsin
- Genetic test for hemochromatosis. Ensure appropriate subject consent is obtained for this test
- Iron Studies:
  - serum ferritin,
  - serum iron,
  - total iron binding capacity

- Consider referral to hepatologist/gastroenterologist
- Consider screen for celiac disease and cystic fibrosis if clinically indicated
- If laboratory tests or ultrasound evidence of biliary tract obstruction, consider obtaining Endoscopic Retrograde Cholangiopancreatography (ERCP) or Magnetic Resonance Cholangiopancreatography (MRCP)

If applicable, request copies of hospital discharge summaries, consultation reports, pathology reports, special studies (e.g. imaging or biopsy), etc.

12.8.4.6 Potential Diagnosis

What diagnosis do the history, clinical course, and laboratory tests suggest?

12.8.4.7 Overall Clinical Impression

What are the investigator's overall clinical impressions (e.g., differential diagnosis, potential alternative causes)?

12.8.4.8 Treatment Plan

What is the plan for treatment and follow-up?

12.8.5 Contacts

If you have any questions, please refer to your Sponsor contact list for the following Merck personnel:

- Clinical Research Associate or Subsidiary Monitor
- Clinical Monitor
- Clinical Scientist

12.8.6 References

- Draft Guidance Document, Hepatotoxicity of Health Products, Ministry of Public Health, Canada, December 2010

  http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/consultation/drug-medic/draft_ebauche_hepatotox_guide_ld-eng.pdf

- FDA Guidance for Industry - Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009

  www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

- Navarro, VJ and JR Senior, 2006, Drug-Related Hepatotoxicity, N Eng J Med, 354(7):731-9.
- Björnsson, E and R Olsson, 2005, Outcome and Prognostic Markers in Severe Drug-Induced Liver Disease, Hepatology, 42(2):481-9.
- Zimmerman, HJ, 1978, Drug-Induced Liver Disease, in: Hepatotoxicity, The Adverse Effects of Drugs and Other Chemicals on the Liver, 1st ed., pp. 351-3, Appleton-Century-Crofts, New York.
- Zimmerman, HJ, 1999, Drug-Induced Liver Disease, in: Hepatotoxicity, The Adverse Effects of Drugs and Other Chemicals on the Liver, 2nd ed., pp. 428-33, Lippincott Williams & Wilkins, Philadelphia.

12.9 Non-Exhaustive List of Drugs and Substances with the Potential to Interfere with CYP3A4 and CYP2A6

Strong CYP3A4 interfering agents are prohibited (in bold and underlined).

A **strong inhibitor** increases the AUC of a substrate for a given CYP by ≥ 5-fold or > 80% decrease in clearance. A **strong inducer** decreases the AUC of a substrate for a given CYP by ≥ 80%.

Strong CYP3A4 inducers	Strong CYP3A4 inhibitors		Moderate CYP3A4 inducers	Moderate CYP3A4 inhibitors	
avasimibe	**boceprevir**	**nefazodone**	amobarbital	atazanavir	fluconazole
carbamazepine	**clarithromycin**	**nelfinavir**	dexamethasone	amiodarone	fosamprenavir
phenytoin	**conivaptan**	**posaconazole**	efavirenz	amprenavir	imatinib
rifampicin	**grapefruit juice**[1]	**ritonavir**	felbamate	aprepitant	miconazole
St John's wort[1]	**indinavir**	**saquinavir**	nevirapine	cimetidine	suboxone
	itraconazole	**telaprevir**	omeprazole	cyclosporine	verapamil
	ketoconazole	**telithromycin**	phenobarbital	darunavir	
	lopinavir	**tipranavir**	pioglitazone	delavirdine	
	mibefradil	**voriconazole**	primidone	diltiazem	
			rifabutin	erythromycin	
			tamoxifen		
			troglitazone		

CYP3A Sensitive substrates				CYP3A Substrates with a Narrow Therapeutic Range	
alfentanil	dronedarone	lovastatin	simvastatin	alfentanil	fentanyl
aprepitant	eletriptan,	lurasidone	sirolimus	astemizole	pimozide
budesonide	eplerenone,	maraviroc	tolvaptan	cisapride	quinidine
buspirone	everolimus	midazolam	tipranavir	cyclosporine	sirolimus
conivaptan	felodipine	nisoldipine	triazolam	dihydroergotamine	tacrolimus
darifenacin	indinavir	quetiapine	vardenafil	ergotamine	terfenadine
darunavir	fluticasone	saquinavir			
dasatinib	lopinavir	sildenafil			

CYP2A6 inducers	CYP2A6 inhibitors	Other CYP2A6 substrates	
phenobarbital	grapefruit juice	coumarin	nicotine
rifampicin	ketoconazole	halothane	quinoline
	methoxsalen	losigamone	SM-12502
	pilocarpine	methoxyflurane	valproic acid
	tranylcypromine		

1. Preparation-dependent

12.10 List of Abbreviations

AE	Adverse Event
AL	Acute Leukemia
ALK	Anaplastic Lymphoma Kinase
ALT	Alanine Aminotransferase
ALL	Acute Lymphoblastic Leukemia
AML	Acute Myeloid Leukemia
AP	Alkaline Phosphatase
AST	Aspartate Aminotransferase
AUC	Area Under The Plasma Concentration Versus Time Curve
BET	Bromodomain and Extraterminal
BID	Twice Daily
BRD	Bromodomain
BRDT	BRD Testis-Specific Protein
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CL	Total Plasma Clearance
Cmax	Peak Concentration
Cmin	Residual Concentration
CNS	Central Nervous System
CT-scan	Computerized Tomography scan
CR	Complete Response
CRPC	Castrate-Resistant Prostate Cancer
DCF	Data Correction Form
DL	Dose Level
DLT	Dose Limiting Toxicity
eCRF	Electronic Case Report Form
EML4	Echinoderm Microtubule-Associated Protein-Like 4
ER	Estrogen Receptor
FISH	Fluorescence In Situ Hybridization
GnRH	Gonadotropin Releasing Hormone
Hb	Hemoglobin
HER2	Human Epidermal Growth Factor Receptor 2
IEC	Independent Ethics Committee
ICF	Informed Consent Form
IHC	Immunohistochemistry
INR	International Normalized Ratio
IRB	Institutional Review Board
KRAS	Kirsten Ras
LDH	Lactate Dehydrogenase
LMWH	Low Molecular Weight Heparin
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
mTPI	Modified Toxicity Probability Interval
NCI-CTCAE	National Cancer Institute -Common Toxicity Criteria for Adverse Events
NMC	NUT Midline Carcinoma
NSCLC	Non-Small Cell Lung Cancer
NUT	Nuclear Protein in Testis
OHM	Other Hematologic Malignancies
OS	Overall Survival
PCWG2	Prostate Cancer Clinical Trials Working Group
PD	Progressive Disease
PFS	Progression-Free Survival
PgR	Progesterone Receptor

PIL	Patient Information Leaflet
PK	Pharmacokinetics
PR	Partial Response
PS	Performance Status
P-TEFb	Positive Transcription Elongation Factor b
QD	Once Daily
RBC	Red Blood Cells
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SAERF	Serious Adverse Event Report Form
SAR	Suspected Adverse Reaction
SCC	Squamous Cell Carcinoma
SD	Stable Disease
SMC	Safety Monitoring Committee
SUSAR	Serious, Unexpected Suspected Adverse Reaction
$t_{1/2}$	Terminal Half-Life
Tmax	Time to Peak Concentration
ULN	Upper Limit of Normal
UPN	Unique Patient Number
UPLC-MS/MS	Ultra Performance Liquid Chromatography, with tandem Mass Spectrometry
Vdss	Volume of Distribution At Steady State
WBC	White Blood Cell

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol). I agree to conduct the trial in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events as defined in Section 7.0 – TRIAL PROCEDURES (Assessing and Recording Adverse Events). I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's Brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	