Time and Events Schedules

NOTE: For Screening Visits, either Table 1 or Table 2 can be used with Table 3.

Table 1: Time and Events Schedule for Treatment Arm A (Ibrutinib + Venetoclax)

TREATMENT ARM A: IBRUTINIB + VENETOCLAX (CYCLE VISIT SCHEDULE ONLY)											
Phase	**Screening**	**Treatment (1 cycle = 28 days)**									**Post-treatment Post-PD Follow-Up**
Study Visits		Cycle 1-3	Cycle 3	Cycle 4				Cycle 5-6	Cycle 7-18	EOT Visit	(every 6 months)
Visit Day (D)	Up to 30 days prior to randomization	D1	D26	D1	D8	D15	D21	D1	D1	30 days (+7) after last dose	±7 days
Drug Administration Treatment (see Section 6)											
Ibrutinib 420 mg daily		⟨---------- Continuous Daily ----------⟩									
Venetoclax 400 mg daily (after ramp up)				Dose Ramp up				Continuous Daily **through Cycle 15**			
Clinic visit for study medication dispensation and accountability check		Required clinic visits on Day 1 of Cycles 1 through 8, 10, 13, 16. During cycles which do not require clinic attendance (eg, Cycles 9, 11, 12, etc), dosing guidelines based on chemistry and hematology cutoffs outlined in Section 6 should be followed. Testing may be done outside of the treating institution.									
TLS risk assessment and prophylaxis			X[a]	X	X	X	X	As needed per investigator's assessment of TLS risk (see Section 6.1.2.2)			
Procedures											
Informed consent	X										
Medical history	X										
Pathology and FISH cytogenetics[b]	X										
IGHV mutational status (central lab)	X										
Buccal swab		Cycle 1 only									
ECG	X[c]										
ECOG Performance Status	X										
CIRS score	X										
Vitals	X										
Weight	X	X		X				X			
Patient reported outcomes (EORTC QLQ-C30, EQ-5D-5L, FACIT-Fatigue)		Perform PROs on Day 1 of Cycles 1, 3, and 5 only. After Cycle 5, follow Disease Evaluation schedule in Table 3.								X	X[d]

TREATMENT ARM A: IBRUTINIB + VENETOCLAX (CYCLE VISIT SCHEDULE ONLY)											
Phase	**Screening**	**Treatment (1 cycle = 28 days)**									**Post-treatment Post-PD Follow-Up**
Study Visits		Cycle 1-3	Cycle 3	Cycle 4				Cycle 5-6	Cycle 7-18	EOT Visit	(every 6 months)
Visit Day (D)	Up to 30 days prior to randomization	D1	D26	D1	D8	D15	D21	D1	D1	30 days (+7) after last dose	±7 days
Laboratory Assessments											
Serum chemistry	X	X[e]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X	
Hematology		X[e]	X	X				X	X	X	
CrCl (Cockcroft-Gault)	X	X[e]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]		
Coagulation panel	X										
Hepatitis testing (see Section 4.2)	X[c]										
Pregnancy test for WOCBP	X	More frequent pregnancy testing may be performed as required by local regulations.									
β_2 microglobulin (local)	X			X					Cycle 10 or DE 3 only	X	
MRD peripheral blood analysis		Cycle 1 only									
Biomarker blood samples[g]		Cycles 1&2 only		X						X	
Predose ibrutinib PK sample (plasma)		Cycles 2&3 only						Cycles 5&6 only			
Disease Evaluations: Will be performed every 12 weeks after randomization through Week 60, then every 16 weeks through Week 156, then every 24 weeks thereafter until disease progression or death. See Table 3 for exact schedule of assessments.											
Ongoing Subject Review											
Concomitant medications	X	Continuous from the signing of ICF until 30 days after the last dose of study treatment or until the start of subsequent anti-leukemic therapy, whichever is first. AEs with onset >30 days after the last dose should be reported if considered related to study treatment.									
Adverse events	X										
Subsequent therapy											X
Survival status (see Section 9.1.4)											X

AE=adverse event; CIRS=Cumulative Illness Rating Scale; CrCl=Creatinine clearance; CR=complete response; CT=computed tomography; D=Day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EORTC QLQ= European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EOT=end-of-treatment; EQ-5D-5L=EuroQol 5 Dimension 5 Level questionnaire; FACIT=Functional Assessment of Chronic Illness Therapy; FISH=fluorescence in situ hybridization; ICF=informed consent form; IGHV=immunoglobulin heavy-chain variable region; LDH=lactate dehydrogenase; MRD=minimal residual disease; PD=progressive disease; PK=pharmacokinetic; PRO=patient-reported outcome; TLS=tumor lysis syndrome; WOCBP=women of childbearing potential

Footnotes:

a. The 12-week CT scan is required to assess TLS risk before the start of venetoclax (See Table 3). Sponsor approval to start Cycle 4 will be dependent on completion of TLS risk assessment.
b. Pathology report, including del17p and del11q by FISH must be sent to Sponsor for review of eligibility prior to randomization.
c. ECG and viral serology results obtained within 60 days of randomization are acceptable.
d. After disease progression, ePRO assessment will be limited to the EQ-5D-5L questionnaire only for the first 2 Post-PD Visits.
e. Laboratory values obtained prior to Cycle 1 Day 1 should be repeated if the blood sample was collected more than 72 hours prior to the anticipated start of study treatment. Test results should satisfy eligibility criteria for treatment to commence.
f. Serum chemistry and creatinine monitoring (see Section 6.1.2.2) must be assessed as part of TLS risk assessment. Abnormalities must be corrected 2-3 days before the start of venetoclax treatment and reassessed prior to each subsequent dose increase. After Cycle 6, additional tests for assessment of TLS risk (ie, uric acid, calcium, phosphate, LDH) may be done on as needed basis as determined by the treating physician.
g. In addition to these timepoints, biomarker samples should be obtained at Disease Evaluation visits during which the first CR response or PD is documented (see Table 3).

Table 2: Time and Events Schedule for Treatment Arm B (Obinutuzumab + Chlorambucil)

TREATMENT ARM B: OBINUTUZUMAB + CHLORAMBUCIL (CYCLE VISIT SCHEDULE ONLY)									
Phase	**Screening**	**Treatment (1 cycle = 28 days)**							**Post-treatment Post-PD Follow-Up**
Study Visits		Cycle 1				Cycle 2-6		EOT Visit	(every 6 months)
Visit Day (D)	Up to 30 days prior to randomization	D1	D2	D8	D15	D1	D15[b]	30 days (+7) after last dose	±7 days
Study Drug Administration (Sec 6)									
Obinutuzumab 100 mg IV		X[a]							
Obinutuzumab 900 mg IV			X[a]						
Obinutuzumab 1000 mg IV				X	X	X			
Chlorambucil 0.5 mg/kg		X			X	X	X[b]		
IRR prophylaxis		X	X	X	X	X			
Procedures									
Informed consent	X								
Medical history	X								
Pathology and FISH cytogenetics[c]	X								
IGHV mutational status (central lab)	X								
Buccal swab		X							
ECG	X[d]								
ECOG	X								
CIRS score	X								
Vitals	X								
Weight	X	X				X			
Patient reported outcomes (EORTC QLQ-C30, EQ-5D-5L, FACIT-Fatigue)		Perform PROs on Day 1 of Cycles 1, 3, 5 only. After Cycle 5, follow Disease Evaluation schedule in Table 3.						X	X[e]
Laboratory Assessments									
Serum chemistry	X	X[f]		X	X	X	X[b]	X	
Hematology	X	X[f]		X	X	X	X[b]	X	
Creatinine clearance	X	X[f]				X			
Coagulation panel	X								
Hepatitis testing (Sec 4.2)	X[d]								
Pregnancy test for WOCBP	X	More frequent pregnancy testing may be performed as required by local regulations.							
$\beta_2$microglobulin	X					Cycle 4 only		X	
MRD peripheral blood analysis		X							

TREATMENT ARM B: OBINUTUZUMAB + CHLORAMBUCIL (CYCLE VISIT SCHEDULE ONLY)									
Phase	**Screening**	**Treatment (1 cycle = 28 days)**							**Post-treatment Post-PD Follow-Up**
Study Visits		Cycle 1				Cycle 2-6		EOT Visit	(every 6 months)
Visit Day (D)	Up to 30 days prior to randomization	D1	D2	D8	D15	D1	D15[b]	30 days (+7) after last dose	±7 days
Biomarker blood samples[g]		X				Cycle 2 & 4 only		X	
Disease Evaluations: will be performed every 12 weeks after randomization through Week 60, then every 16 weeks through Week 156, then every 24 weeks thereafter until disease progression or death. See Table 3 for exact schedule of assessments.									
Ongoing Subject Review									
Concomitant medications	X	Continuous from the signing of ICF until 30 days after the last dose of study treatment or until the start of subsequent anti-leukemic therapy, if earlier. AEs with onset >30 days after the last dose should be reported if considered related to study treatment.							
Adverse events	X								
Subsequent therapy									X
Survival status (see Section 9.1.4)									X

AE=adverse event; CIRS=Cumulative Illness Rating Scale; CR=complete response; D=Day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EORTC QLQ=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EOT=end-of-treatment; EQ-5D-5L=EuroQol 5 Dimension 5 Level questionnaire; FACIT=Functional Assessment of Chronic Illness Therapy; FISH=fluorescence in situ hybridization; ICF=informed consent form; IGHV=immunoglobulin heavy-chain variable region; IRR=infusion-related reaction; IV=intravenous; MRD=minimal residual disease; PD=progressive disease; PRO=patient-reported outcome; WOCBP=women of childbearing potential

Footnotes:

a. Split first dose between Day 1 (100 mg) and Day 2 (900 mg). For subjects who tolerate the first 100 mg well and required no dose interruption or modification of the infusion rate, the full dose may be given on Day 1 (See Section 6.2.1.1) at investigator's discretion.
b. Pre-dose laboratory tests may be done outside the treating institution on Day 15, Cycles 2-6. The investigator is required to assess these results, recommend dose interruptions or reductions as needed, and to approve home self-administration of chlorambucil on Day 15, Cycles 2-6.
c. Pathology report, including del17p and del11q by FISH must be sent to Sponsor for review of eligibility prior to randomization.
d. ECG and viral serology results obtained within 60 days of randomization are acceptable.
e. After disease progression, ePRO assessment will be limited to the EQ-5D-5L questionnaire only for the first 2 Post-PD Visits.
f. Laboratory values obtained prior to Cycle 1 Day 1 should be repeated if the blood sample was collected more than 72 hours prior to the anticipated start of study treatment. Test results should satisfy eligibility criteria for treatment to commence.
g. In addition to these timepoints, biomarker samples should be obtained at Disease Evaluation visits during which the first CR response or PD is documented (see Table 3)

Table 3: Time and Events Schedule for Treatment and Post-Treatment Disease Evaluations Prior to Disease Progression Arm A and B[a]

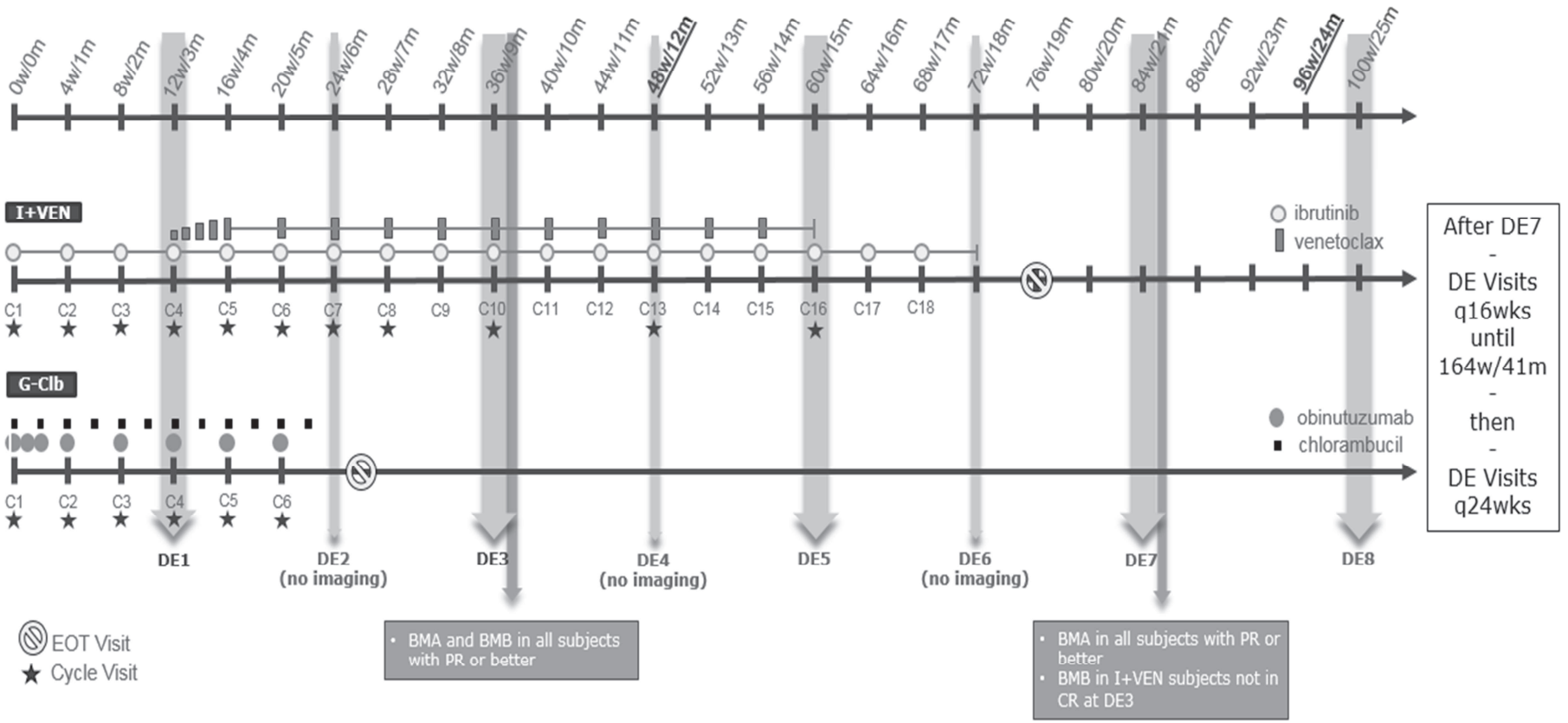
	Screening	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Weeks 84 through 164	Week 164 onward
Disease Evaluation (DE)	Up to 30 days prior to randomization	DE 1	DE 2	DE 3	DE 4	DE 5	DE 6	DE 7	DE -12 (every 16 Weeks)	DE 12 onward (every 24 Weeks)
	Note: DE1 has window of -7 days; all other DE visits have a window of ±7 days.									
CT Scan	X[b]	X[c]		X		X		X	X	X
Physical examination	X	X	X	X	X	X	X	X	X	X
Disease-related symptoms	X	X	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X	X
Bone marrow aspirate	X[b]			X[d]				X[d]		
Bone marrow biopsy	X[b]			X[d]				X[d]		
MRD in subjects with PR or better										
Peripheral blood MRD		X	X	X	X	X	X	X	X	X
Bone marrow aspirate MRD	X[b]			X[d]				X[d]		
Patient reported outcomes (EORTC QLQ-C30, EQ-5D-5L, FACIT-Fatigue)			X	X	X	X	X	X	X	X
Biomarker blood samples[e]	X			X						

CR=complete response; CT=computed tomography; DE=Disease Evaluation; EORTC QLQ= European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L=EuroQol 5 Dimension 5 Level questionnaire; FACIT=Functional Assessment of Chronic Illness Therapy; MRD=minimal residual disease; PR=partial response; PD=progressive disease; TLS=tumor lysis syndrome.

Footnotes:

a. After disease progression, follow Post-Treatment post-PD Follow-up schedule of assessments in each respective arm (Tables 1 and 2).
b. Standard of care CT scans meeting the Imaging Acquisition Guidelines standard done within 60 days of randomization and a bone marrow biopsy and aspirate done within 90 days of randomization may be used for screening. For subjects undergoing a bone marrow biopsy and aspirate during the screening, a sample of the aspirate and biopsy should be collected for biomarker assays and MRD testing. Archived bone marrow slides for biomarkers are acceptable.
c. The 12-week CT scan is critical to assess TLS risk at the end of Cycle 3. This scan is required for both Treatment Arms A and B.
d. For all subjects with a response of PR or better, a bone marrow aspirate and biopsy must be obtained and central assessment of bone marrow aspirate for MRD must be performed at Disease Evaluation 3. At Disease Evaluation 7, a central bone marrow aspirate MRD assessment is required in all subjects with a response of PR or better. Bone marrow biopsy and aspirate for local evaluations are only required for subjects on the I+VEN arm who were not confirmed CR at Disease Evaluation 3. For subjects with a suspected PD based on new onset cytopenia, a bone marrow aspirate and biopsy should be obtained to confirm PD.
e. At Disease Evaluation 3 and at any Disease Evaluation visit during which the first CR response or PD is documented.

Figure 1: Disease Evaluation and Treatment Schedule



Abbreviations: BMA=bone marrow aspirate; BMB=bone marrow biopsy; C=Cycle; CR=complete response; DE=Disease Evaluation; EOT=end-of-treatment; G-Clb=obinutuzumab and chlorambucil; I+VEN=ibrutinib and venetoclax; m=month; PR=partial response; w=week

Notes:

- 0w/0m corresponds to date of randomization.
- Disease Evaluation visits will occur every 12 weeks until Disease Evaluation 7 at 84 weeks, then every 16 weeks until 164 weeks, then every 24 weeks until progression or death.
- Imaging at 12 weeks, then every 24 weeks x 3, every 16 weeks x 5, then every 24 weeks.