BC Cancer Protocol Summary for Treatment of Relapsed/Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma Using Venetoclax

Protocol Code	*ULYVENETO*
Tumour Group	*Lymphoma*
Contact Physicians	*Dr. Alina Gerrie, Dr. Laurie Sehn*
Contact Pharmacist	*Louisa Pang*

ELIGIBILITY:

- Relapsed/refractory chronic lymphocytic leukemia or small lymphocytic lymphoma with or without chromosome 17p deletion, who have progressed on or are intolerant to B-cell receptor pathway inhibitors (BTK-inhibitors, such as ibrutinib and/or PI3-kinase inhibitors, such as idelalisib)
- Symptomatic disease requiring systemic therapy
- A Compassionate Access Program (CAP) approval is required prior to the initiation of treatment (please refer to https://cap.phsa.ca/).

EXCLUSION:

- Creatinine clearance less than 30 mL/min (Cockcroft-Gault formula)*****
- Platelet count less than 30 x 10^9/L unless disease-related
- Absolute neutrophil count (ANC) less than 1.0 x 10^9/L may be considered a relative contraindication unless disease-related. Consider giving filgrastim.
- Bilirubin greater than 3 x upper limit of normal (ULN)
- Active and uncontrolled autoimmune cytopenias
- Strong CYP3A4 inhibitors contraindicated during initiation and dose ramp-up phase

*******In clinical trials, venetoclax was given to patients with a CrCl ≥ 50 mL/min. The Canadian product monograph decreases this threshold to ≥ 30 mL/min and mentions that a CrCl < 80 mL/min may be at an increased risk of tumour lysis syndrome (TLS).*

TESTS:

- **Baseline** (required, within 72 h of first treatment): CBC and diff, potassium, calcium, magnesium, phosphate, uric acid, creatinine, urea, bilirubin, ALT, LDH, albumin, pregnancy test prior to treatment in females of child-bearing potential
- **Baseline** (required, but results do not have to be available to proceed with first treatment; results must be checked before proceeding with cycle 2): HBsAg, HBcoreAb
- **Prior to each dose increment during ramp-up phase (weeks 1 to 5)**: potassium, calcium, phosphate, uric acid, creatinine, LDH, albumin
- **Tumour lysis syndrome (TLS) monitoring:** potassium, calcium, phosphate, uric acid, creatinine, LDH, albumin based on tumour burden/TLS risk (See **Table 1** below). **TLS labs must be drawn STAT at a laboratory capable of rapid turnaround time (e.g. BC Cancer or hospital laboratory)**
- **Each time seen by physician post ramp-up phase (week 6 onwards):** CBC and diff, creatinine, bilirubin, ALT

PREMEDICATIONS:

- Antiemetic protocol for Low emetogenic chemotherapy (see SCNAUSEA)

SUPPORTIVE MEDICATIONS:

If HBsAg or HBcoreAb positive, start lamiVUDine 100 mg PO daily for the duration of chemotherapy and continue for one year from treatment completion for patients who are HBsAg positive and for six months for patients who are HBcoreAb positive.

Tumour lysis syndrome (TLS), including fatal events and renal failure requiring dialysis, has been reported in patients with medium or high tumour burden, but the incidence is reduced when the venetoclax dose is gradually increased. It is mandatory that electrolytes are monitored as recommended as TLS requires prompt management (**see Appendix I**). TLS can occur as early as 6-8 hours after the first dose and after each dose increase.

Table 1: Recommended TLS monitoring and prophylaxis based on tumour burden:

Tumour Burden		**Prophylaxis**		**Blood chemistry monitoring**
		Hydration	**Anti-hyperuricemic**	**Setting and Frequency of Assessments**
Low	All LN***** less than 5 cm **AND** ALC****** less than 25 x 10^9/L	Oral: 1.5 to 2 L daily (8 glasses) Start 48 h prior to 1st dose and continue throughout the first 5 weeks of therapy	Allopurinol 300 mg PO daily until dose escalation is complete and at physician discretion Start 72 h prior to 1st dose	**Outpatient:** • Pre-dose at each dose increment • 6 h and 24h post first dose of 20 mg and 50 mg
Medium	Any LN***** 5 cm to less than 10 cm **OR** ALC****** greater than or equal to 25 x 10^9/L AND any LN less than 5 cm	Oral: 1.5 to 2 L daily (8 glasses) Start 48 h prior to 1st dose, and continue throughout the first 5 weeks of therapy. Consider additional IV fluids as needed		**Outpatient:** • Pre-dose at each dose increment • 6h and 24h post first dose of 20 mg and 50 mg • Consider hospitalization, if CrCl± 50-80 mL/min or if patient unable to drink 2L of oral fluids at first dose of 20 mg and 50 mg (see High Risk category)

Tumour Burden		Prophylaxis		Blood chemistry monitoring
		Hydration	Anti-hyperuricemic	Setting and Frequency of Assessments
High	Any LN***** greater than or equal to 10 cm **OR** ALC****** greater than or equal to 25 x 10^9/L AND any LN greater than or equal to 5 cm **OR** CrCl ± 30-50 mL/min	Oral: 1.5 to 2 L daily (8 glasses) Start 48 h prior to 1st dose, and continue throughout the first 5 weeks of therapy and IV NS (150 to 200 mL/hr, as tolerated)	Allopurinol 300 mg PO daily until dose escalation complete and at physician discretion Start 72 h prior to 1st dose Consider rasburicase 3 mg IV x 1, may repeat Q24H prn **For patients on rasburicase, blood sample for uric acid must be placed on ice while awaiting assay**	**Inpatient:** First dose of 20 mg and 50 mg • Pre-dose, 4h, 8h, 12h and 24h post first dose of 20 mg and 50 mg **Outpatient:** Subsequent ramp-up doses • Pre-dose, 6h, and 24h post dose

*****LN= lymph node
******ALC= absolute lymphocyte count

±Cockcroft-Gault Equation:

$$\text{Estimated creatinine clearance: CrCl (mL/min)} = \frac{\text{N (140 - age) wt (kg)}}{\text{serum creatinine (micromol/L)}}$$

N = 1.23 male
N = 1.04 female

TREATMENT:

Due to the risk of TLS, venetoclax dosing must be initiated carefully according to a 5 week ramp-up schedule up to the recommended dose of 400 mg PO once daily. Patients who show signs of TLS should have their dose held or if appropriate, kept the same for more than one week, until it is safe to dose escalate. Treatment continues until disease progression or unacceptable toxicity.

For low or medium risk TLS patients, the start date must be on a Thursday, and patients must pick up their venetoclax before Thursday.

For high risk TLS patients, start date is not restricted to a Thursday.

Ramp-up phase: Weeks 1-5 for low, medium, high risk TLS patients

Week	Drug	Dose	BC Cancer Administration Guideline
1	Venetoclax±	20 mg once daily	PO
2		50 mg once daily	
3		100 mg once daily	
4		200 mg once daily	
5		400 mg once daily	

Post ramp-up phase: Week 6 onwards for low, medium, high risk TLS patients

Week	Drug	Dose	BC Cancer Administration Guideline
6 onwards	Venetoclax	400 mg once daily	PO

± Lab results must be reviewed by pharmacist or MD, at the time points indicated below, before next dose can be authorized in person or by phone (**baseline labs** reviewed by **MD**, ramp-up and **TLS labs** reviewed by **pharmacist**):

- baseline, within 72h of initiating treatment (day 1)
- before each dose increase at 50 mg, 100 mg, 200 mg and 400 mg (weeks 2 to 5)
- the day after the first 20 mg dose (24h) and 50 mg dose (24h) increase (weeks 1 and 2)
- for high risk patients only, 24 h after each additional dose increase (100 mg, 200 mg, and 400 mg, at weeks 3, 4 and 5)

For **low or medium risk TLS** patients, see **Appendix II, Table 1** for frequency of laboratory monitoring by pharmacist and patient follow-up schedule.

- If baseline labs adequate to proceed, patient to take first dose at **6 am on a Thursday in order for labs and RN phone call to not fall on a statutory holiday or weekend.**
- Outpatient STAT **TLS labs** at **6 h** (12 noon) and at approximately **24 h** (8 am the second day)
- Results must be reviewed immediately by the pharmacist to assess for signs of TLS and determine whether prompt management or admission is required
- A pharmacist will contact the patient **after the 24h lab results are reviewed** for instructions on whether to proceed with the next dose

For **high risk TLS** patients, see **Appendix II, Table 2** for frequency of laboratory monitoring by pharmacist and patient follow-up schedule.

- Treatment is not restricted to a Thursday start date. When patients are discharged home, supply enough tablets, so that the start day of a new dose occurs on a Thursday to ensure that labs will be monitored by pharmacy.

DOSE MODIFICATIONS:

Venetoclax Dose at Interruption	Recommended Restarting Dose
20 mg once daily	10 mg once daily
50 mg once daily	20 mg once daily
100 mg once daily	50 mg once daily
200 mg once daily	100 mg once daily
300 mg once daily	200 mg once daily
400 mg once daily	300 mg once daily

1. Tumour Lysis Syndrome (TLS)

- Changes in blood chemistries that require prompt management can occur as early as 6-8 hours after the first dose of venetoclax and after each dose increase
- Reduced renal function (CrCl ≤ 80 mL/min) increases the risk for TLS
- Electrolytes must be corrected to within normal limits prior to proceeding with next dose of venetoclax or any dose increases during the 5-week ramp-up phase
- See **Appendix I** for TLS management strategies

Event	Action
Abnormal blood chemistry outside normal parameters for any of the following: • Elevated potassium • Low calcium (corrected for albumin*****) • Elevated phosphate • Elevated uric acid • Serum creatinine increase of greater than 20 micromol/L from baseline	Hold venetoclax. Correct abnormalities. If resolved within 24-48h, resume at same dose.
Abnormal blood chemistry lasting more than 48 hours ***OR*** **Clinical TLS** (presence of **laboratory TLS**† plus any of the following): • cardiac arrhythmia, symptomatic hypocalcemia, seizures, increased creatinine level of 26.5 micromol/L or single value greater than 1.5 times ULN	Hold until resolved; then resume at a reduced dose (see Dose Modification table above). Continue the reduced dose for 1 week before continuing with dose escalation.

***** Corrected calcium (mmol/L) = total calcium (mmol/L) + (0.02 x [40 – albumin in g/L])

† **Laboratory TLS** (2 or more metabolic abnormalities during the same 24 hour period):

- Uric acid greater than or equal to 476 micromol/L
- Phosphate greater than or equal to 1.45 mmol/L
- Potassium greater than or equal to 6 mmol/L
- Corrected calcium less than or equal to 1.75 mmol/L

2. Hematological and Non-Hematological Toxicities

Toxicity	Venetoclax
ANC less than 1.0 x 10^9/L*	Hold until ANC greater than or equal to 1.0 x 10^9/L, then resume at same dose
Platelets less than 30 x 10^9/L*	Hold until platelets greater than or equal to 30 x 10^9/L, then resume at same dose
Non-hematological toxicity greater than or equal to Grade 3	Hold until improvement to grade 1 toxicity or baseline, then resume at same dose.

*For 2nd and subsequent occurrences, resume treatment at a reduced dose following the above Dose Modification table.

- Consider discontinuing treatment for patients needing dose reduction to less than 100 mg once daily for more than 2 weeks.

Hepatic Impairment	Dosing recommendation
Mild to moderate (total bilirubin greater than 1.5 to less than 3 x ULN)	No dose adjustment
Severe (total bilirubin greater than 3 x ULN)	Discontinue

3. Drug Interactions

Venetoclax is a major CYP3A4 substrate and a substrate of P-glycoprotein. Concurrent administration of drugs which are **strong CYP 3A4 inhibitors are contraindicated at initiation and during the dose ramp-up phase** due to increased serum concentration of venetoclax and potential increased risk of TLS.

CYP3A4 inducers may decrease serum concentration of venetoclax.
P-glycoprotein inhibitors (P-gp) may increase serum concentration of venetoclax.

Agent Initiated	At initiation and dose ramp-up	After dose-ramp up is completed
Strong CYP3A4 inhibitors	Contraindicated	Reduce venetoclax dose by 75%. Resume standard venetoclax dosing 2 to 3 days after CYP3A4 inhibitor is discontinued.
Moderate CYP3A4 inhibitors	Avoid if possible, but if unavoidable, reduce venetoclax dose by at least 50%. Monitor patients more closely for signs of toxicities. Resume standard venetoclax dosing 2 to 3 days after CYP3A4 inhibitor is discontinued.	
Weak CYP3A4 inhibitors	No dose adjustment needed	
Strong and moderate CYP3A4 inducers	Avoid. Consider alternative treatments with less CYP3A4 induction.	

P-glycoprotein inhibitors	Avoid if possible, but if unavoidable, reduce venetoclax dose by at least 50%. Monitor patients more closely for signs of toxicities. Resume standard dosing one day after discontinuation of P-gp inhibitor. **Note:** an exception is made for **Azithromycin**, where dose adjustments of venetoclax are not required.

PRECAUTIONS:

1. **Tumour lysis syndrome (TLS):** TLS has been reported and the risk is greatest during the dose ramp-up phase. Patients should be stratified as low, medium, or high risk based on their lymph node size (LN), absolute lymphocyte count (ALC), and comorbidities including renal dysfunction. All patients require prophylaxis for TLS using hydration beginning 48 hours and anti-hyperuricemic agents beginning 72 hours prior to initiation of therapy. Hospitalization is recommended for high risk patients, medium risk patients with abnormal CrCl and any risk patients with CrCl ≤ 50 mL/min. Hospitalization may be considered for those with additional risk factors for TLS (CrCl ≤ 80 ml/min, unable to drink 1.5-2 L per day, unsuitable for outpatient treatment and lab monitoring, or at physician discretion). It is mandatory that electrolytes are monitored as TLS requires prompt management (see **Appendix I** for management recommendations). **For outpatients, TLS labs must be reviewed at 6 hours and 24 hours after the first 2 dose escalations (20 mg and 50 mg) for low or medium risk patients and after all dose escalations for high-risk patients (100 mg, 200 mg, and 400 mg). Patients must be instructed to wait to take the second dose until approval is given (by phone). See Appendix II, Tables 1 and 2 for frequency of laboratory monitoring and patient follow-up schedule.**
2. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively. Refer to BC Cancer Febrile Neutropenia Guidelines.
3. **Hepatitis B Reactivation:** All lymphoma patients should be tested for both HBsAg and HBcoreAb. If either test is positive, such patients should be treated with lamiVUDine 100 PO daily for the entire duration of chemotherapy and continue for one year from treatment completion for patients who are HBsAg positive and for six months for patients who are HBcoreAb positive.. Such patients should also be monitored with frequent liver function tests and hepatitis B virus DNA at least every two months. If the hepatitis B virus DNA level rises during this monitoring, management should be reviewed with an appropriate specialist with experience managing hepatitis and consideration given to halting chemotherapy.
4. **Drug interactions:** Venetoclax is a major CYP3A4 substrate and a substrate of P-glycoprotein. Concurrent administration of drugs which are strong CYP 3A4 inhibitors is contraindicated at initiation and during the dose ramp-up phase, due to increased serum concentration of venetoclax and potential increased risk of TLS. See Drug Interactions in Dose Modification section above.
5. **Pregnancy:** Venetoclax is not recommended for use in pregnancy. Fetotoxicity is likely. Women of childbearing potential should undergo pregnancy testing before initiating treatment and use adequate contraception during treatment and for at least 30 days after the last dose

Call Dr. Alina Gerrie, Dr. Laurie Sehn or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

1. Roberts et al. Targeting BCL-2 with venetoclax in relapsed chronic lymphocytic leukemia. NEJM 2016; 374(4):311-322
2. Jones JA et al. Venetoclax for chronic lymphocytic leukaemia progressing after ibrutinib: an interim analysis of a multicentre, open-label, phase 2 trial. Lancet Oncol 2018; 19(1):65-75. doi: 10.1016/S1470-2045(17)30909-9
3. Coutre S et al. Venetoclax for patients with chronic lymphocytic leukemia who progressed during or after idelalisib therapy. Blood 2018; 131(15) 1704-1711
4. Stilgenbauer et al. Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label, phase 2 study. Lancet Oncol 2016; 17(6): 768-778
5. Mato et al. Optimal sequencing of ibrutinib, idelalisib, and venetoclax in chronic lymphocytic leukemia: results from a multicenter study of 683 patients. Ann Oncol. 2017; 28(5): 1050-1056. doi: 10.1093/annonc/mdx031
6. AbbVie Corporation. VENCLEXTA® product monograph. St-Laurent, Quebec; 27 September 2016
7. AbbVie Inc. VENCLEXTA® product monograph. North Chicago, IL; November 2018.
8. Howard et al. the Tumor Lysis Syndrome. NEJM 2011; 364(19): 1844-1854
9. Coiffer et al. Guidelines for the Management of Pediatric and Adult Tumor Lysis Syndrome: An Evidence-Based Review. JCO 2008; 26(16): 2767-2778
10. Tumor Lysis Syndrome (TLS) in Adult Patients from MD Anderson Centre. https://www.mdanderson.org/content/dam/mdanderson/documents/for-physicians/algorithms/clinical-management/clin-management-tumor-lysis-web-algorithm.pdf
11. Agarwal et al. Effect of Azithromycin on Venetoclax Pharmacokinetics in Health Volunteers: Implications for Dosing Venetoclax with P-gp Inhibitors. Advances in Therapy 2018; 35(11):2015-2023

APPENDIX I:

Manage Tumour Lysis Syndrome (TLS) according to institution guidelines. If no local guidelines, may use the following. Consider hospital admission, if needed for cardiac monitoring or IV medications/hydration.

Suggested Guide for Management of Tumour Lysis Syndrome (TLS) (adapted from MD Anderson TLS guidelines[10])

Electrolyte Abnormality	Management Recommendations
Hyperkalemia	
Mild (greater than upper limit of normal to less than 6 mmol/L)	• Restrict potassium intake (avoid IV and PO potassium, limit dietary intake) • Sodium polystyrene (Kayexalate®) o 15-30 grams PO o Repeat as needed depending on follow-up potassium levels • Consider ECG and cardiac rhythm monitoring at physician discretion
Moderate (6-7 mmol/L) **and** asymptomatic	• Restrict potassium intake (avoid IV and PO potassium, limit dietary intake) • ECG and cardiac rhythm monitoring • Sodium polystyrene (Kayexalate®) o 15-30 grams PO o Repeat every 4 to 6 hours depending on follow-up potassium levels
Severe (greater than 7 mmol/L **and/or** symptomatic)	Same as moderate plan plus: • Concurrent ECG changes: calcium gluconate 1 g via slow IV infusion; may be repeated after 5-10 minutes if ECG changes persist • To temporarily shift potassium intracellularly: • IV insulin and dextrose ➢ Give 10 units of regular insulin in 500 mL of D10W infused IV over 60 minutes ➢ Monitor blood glucose closely • Sodium bicarbonate ➢ Give 50 mEq via slow IV infusion ➢ Can be used if patient is acidemic; however sodium bicarbonate and calcium should not be administered through the same lumen • Salbutamol ➢ Give 10-20 mg in 4 mL saline via nebulizer over 20 minutes or 10-20 puffs via inhaler over 10-20 minutes ➢ Avoid in patients with acute coronary disease

Electrolyte Abnormality	Management Recommendations
Hyperphosphatemia	
Moderate (greater than or equal to 1.94 mmol/L)	• Restrict phosphorus intake (avoid IV and PO phosphorus; limit dietary sources) • Administer phosphate binder: o Sevelamer (Renagel®, Renvela®) 800-1600 mg PO three times a day with meals o Lanthanum carbonate (Fosrenol®) 500-1000 mg PO three times a day with meals o Aluminum hydroxide tablet 300 mg PO three times a day with meals, may increase dose to 600 mg PO three times a day (avoid in patients with renal dysfunction) o Aluminum hydroxide 64 mg/mL suspension 15 mL PO three times a day with meals, may increase dose to 30 mL four times a day based on phosphate level (avoid in patients with renal dysfunction)
Severe	Dialysis may be needed in severe cases
Hypocalcemia (calcium less than or equal to 1.75 mmol/L or ionized calcium less than or equal to 0.8 mmol/L)	
Asymptomatic	• No therapy • To avoid calcium phosphate precipitation, asymptomatic patients with acute hypocalcemia and hyperphosphatemia should not be given calcium repletion until phosphorous level has normalized
Symptomatic	Calcium gluconate 1 g via slow IV infusion with ECG monitoring
Uremia (renal dysfunction)	
	• Fluid and electrolyte management • Uric acid and phosphate management • Adjust doses for renally excreted medications • Dialysis

APPENDIX II.

Table 1. Monitoring for <u>Low or Medium Risk TLS Patients.</u> Pharmacist reviews labs and contacts patient to take venetoclax dose.

	Day 1	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Week 1 **20 mg** ▪ baseline lab	6 AM dose ▪ lab at 12 noon ▪ review bloodwork and notify MD if abnormal	▪ lab at 8 am ▪ review bloodwork and notify MD if abnormal. If normal, contact patient to take week 1 day 2 dose	8 AM dose	8 AM dose	8 AM dose	8 AM dose ▪ RN call to remind patient to go for lab the next day (pre ramp-up lab)	8 AM dose ▪ lab before 12 noon ▪ review bloodwork and notify MD if abnormal. If normal, contact patient to take week 2 day 1 dose (50 mg) the following day
Week 2 **50 mg**	6 AM dose ▪ lab at 12 noon ▪ review bloodwork and notify MD if abnormal	▪ lab at 8 am ▪ review bloodwork and notify MD if abnormal. If normal, contact patient to take week 2 day 2 dose	8 AM dose	8 AM dose	8 AM dose	8 AM dose ▪ RN call to remind patient to go for lab the next day (pre ramp-up lab)	8 AM dose ▪ lab before 12 noon ▪ review bloodwork and notify MD if abnormal. If normal, contact patient to take week 3 day 1 dose (100 mg) the following day
Week 3 **100 mg**	8 AM dose	8 AM dose	8 AM dose	8 AM dose	8 AM dose	8 AM dose ▪ RN call to remind patient to go for lab the next day (pre ramp-up lab)	8 AM dose ▪ lab before 12 noon ▪ review bloodwork and notify MD if abnormal. If normal, contact patient to take week 4 day 1 dose (200 mg) the following day
Week 4 **200 mg**	8 AM dose	8 AM dose	8 AM dose	8 AM dose	8 AM dose	8 AM dose ▪ RN call to remind patient to go for lab the next day (pre ramp-up lab)	8 AM dose ▪ lab before 12 noon ▪ review bloodwork and notify MD if abnormal. If normal, contact patient to take week 5 day 1 dose (400 mg) the following day
Week 5 onwards **400 mg**	8 AM dose	8 AM dose	8 AM dose	8 AM dose	8 AM dose	8 AM dose	8 AM dose

Table 2. Monitoring for <u>High Risk TLS patients.</u> Unless otherwise specified, lab review is done by pharmacist and pharmacist contacts patient to take venetoclax dose.

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Week 1 **20 mg** ▪ baseline lab	Inpatient ▪ labs 4h, 8h, 12h and 24 h post dose (monitoring done by ward)	Inpatient for 2nd dose ▪ ward team to review 24h lab post 20 mg dose and notify MD if abnormal. If normal, give patient week 1 day 2 dose and may be discharged home or at MD discretion	8 AM dose	8 AM dose	8 AM dose	8 AM dose ▪ RN call to remind patient to go for lab the next day (pre ramp-up lab)	8 AM dose ▪ lab before 12 noon ▪ review bloodwork and notify MD if abnormal.
Week 2 **50 mg**	Inpatient ▪ labs 4h, 8h, 12h and 24 h post dose (monitoring done by ward)	Inpatient for 2nd dose ▪ ward team to review 24h lab post 50 mg dose and notify MD if abnormal. If normal, give patient week 2 day 2 dose and may be discharged home or at MD discretion	8 AM dose	8 AM dose	8 AM dose	8 AM dose ▪ RN call to remind patient to go for lab the next day (pre ramp-up lab)	8 AM dose ▪ lab before 12 noon ▪ review bloodwork and notify MD if abnormal. If normal, contact patient to take week 3 day 1 dose (100 mg) the following day
Week 3 **100 mg**	6 AM dose ▪ lab at 12 noon ▪ review bloodwork and notify MD if abnormal	▪ lab at 8am ▪ review bloodwork and notify MD if abnormal. If normal, contact patient to take week 3 day 2 dose	8 AM dose	8 AM dose	8 AM dose	8 AM dose ▪ RN call to remind patient to go for lab the next day (pre ramp-up lab)	8 AM dose ▪ lab before 12 noon ▪ review bloodwork and notify MD if abnormal. If normal, contact patient to take week 4 day 1 dose (200 mg) the following day
Week 4 **200 mg**	6 AM dose ▪ lab at 12 noon ▪ review bloodwork and notify MD if abnormal	▪ lab at 8am ▪ review bloodwork and notify MD if abnormal. If normal, contact patient to take week 4 day 2 dose	8 AM dose	8 AM dose	8 AM dose	8 AM dose ▪ RN call to remind patient to go for lab the next day (pre ramp-up lab)	8 AM dose ▪ lab before 12 noon ▪ review bloodwork and notify MD if abnormal. If normal, contact patient to take week 5 day 1 dose (400 mg) the following day
Week 5 onwards **400 mg**	6 AM dose ▪ lab at 12 noon ▪ review bloodwork and notify MD if abnormal	▪ lab at 8am ▪ review bloodwork and notify MD if abnormal. If normal, contact patient to take week 5 day 2 dose	8 AM dose	8 AM dose	8 AM dose	8 AM dose	8 AM dose