Amendment **Source of change**
Clarification of contraceptive requirements in Inclusion criteria 8b and 9
Inclusion Criterion #7, change from > to <450 ms
Exclusion criterion #4 added “active” before “infection
Exclusion criterion #7 (originally #6): added “A CPT score of >6 based on screening laboratory results.”
Exclusion criterion #11 (originally #10): change the wording to” Significant renal dysfunction, defined as serum creatinine concentration ≥1.5 times the ULN or an estimated glomerular filtration rate (eGFR) < 80 mL/min at screening, based on the Cockcroft-Gault equation.”
Exclusion criterion #12 (originally #11): after “viral hepatitis” added “(not including HBV or HCV)
Prohibited medications exclusion criterion #20, (originally #19): added “unless otherwise described in the protocol (i.e. Ondansetron)
Study population and number of patients: changed “Up to” to “Approximately”
Study Assessments, Pharmacokinetics, timing of sampling: added text for clarification
Overall study design/PK: added text for clarification
Pharmacokinetic sampling: added text for clarification
Prohibited medications clarification: added “(unless otherwise described within protocol as allowed (i.e. Ondansetron)”
Prohibited medications clarification: added” • Use of ondansetron for symptomatic treatment of nausea is allowed; prudent medical judgment should be applied as to the dose and duration of its use.”
Change of description of frequencies of most common AEs: added Table 2 to include AEs reported in Study 12-DK-0016
Addition of Table 2, with frequencies of most common AEs
Dose of Peg- IFN-α2a used in Study EIG-300/LOWR-1: added dose and frequency of the use of PEG-INF α2a
Early withdrawal visit clarification: added text for clarification
Product storage conditions change: change the lower limit of temperature from 20°C (68°F) to15°C (59°F)
Source of Ritonavir clarification: added text for clarification
Study treatment distribution description change: change the text to:” Patients will be provided appropriate quantities of study drug based on dosage, for a period of 2 or 4 weeks. Lonafarnib and ritonavir will be supplied in separate, clearly marked bottles. Patients will be provided quantities sufficient for a 2 week or 4-week period based on the individual patient’s titration schedule.”
Dose titration clarification: changed to“. The treatment duration at the initial tolerated dose of lonafarnib/ should be maintained for at least 4 weeks before upward titration
Definition of Stable dose: remove “taken without interruption”

Amendment **Source of change**
Evaluation of tolerability: weight loss: added ". If a patient experiences unintentional weight loss of at least 3 kg or 5% from baseline weight, whichever is greater, the Investigator should assess for factors contributing to weight loss and encourage optimum nutrition. The lonafarnib dose may be decreased according to the dose down-titration scheme at the Investigator's discretion. If a patient experiences unintentional study-drug related weight loss of at least 6 kg or 10% from baseline weight, whichever is greater, and this is considered to be study drug related, then the patient's lonafarnib dose must be decreased according to the dose down-titration scheme. In this instance, "weight loss" should be entered as an AE and outcome captured as "resulted in dose reduction."
Concomitant Therapies: added "Use of any prescription, nonprescription or natural medications (herbal medicines) is excluded unless use of such medication is medically necessary; as drug-drug interactions with lonafarnib and ritonavir and other drugs have not been fully explored; all concomitant medications should be appropriately monitored for possible interactions throughout the course of the study."
Contraception requirements clarification: added text and time requirement for clarification
Electrocardiograms: removed the digital copy requirement
Clinical chemistry testing, TSH and cannabinoid testing added
Blood volumes drawn during study: Blood alcohol, T3, T4,TSH added to tests
Addition of Triiodothyronine (T3) and thyroxine (T4) to list of blood samples in screening visit.
Addition of trough PK blood sample to Week 2, 4, 6 treatment visits.
Addition of PMBC analysis sample to Week 4, Week 28, and Weeks 36 and 48
Clarification of timing of PBMC blood draw to Week 12 only
Clarify PK sampling timepoints during Weeks 8, 12 and 16.
Add ophthalmic exam to Early Termination Visit
Clarify determination of sample size
Clarify medium for SAE reporting, and email addresses
Clarify informed consent for pregnancy information.
Appendix A, schedule of study assessments: Addition of T3, T4, HBeAg, HBeAb, blood alcohol to screening visit. Additional PBMC blood samples on weeks 4, 24, 28, 36 and 48
Appendix A, schedule of study assessments: added "as soon as possible"
Appendix A, schedule of study assessments: added text for clarification
Appendix A, schedule of study assessments: added "An early termination visit ophthalmic exam is only required if the early termination occurs between weeks 12 and 24 of the dosing period."