Inklusionskriterier:	Ja	Nej
1. Male or female subjects are at least 18 years of age at the time of signing the informed consent form (ICF).		
2. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1 or 2.		
3. Subjects have diagnosis of primary myelofibrosis (PMF) according to the 2016 World Health Organization (WHO) criteria, or diagnosis of post-ET (PET-MF) or post-PV myelofibrosis (PPV-MF) according to the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) 2007 criteria.		
4. Palpable spleen of at least 5 cm from the left costal margin (LCM) to the point of greatest splenic protrusion or enlarged spleen volume of at least 450 cm3 per MRI or CT scan at baseline (an MRI/CT scan up to 8 weeks prior to first dose of study treatment can be accepted).		
5. Have been treated with ruxolitinib for at least 24 weeks prior to first dose of study treatment.		
6. Are stable (no dose adjustments) on the prescribed ruxolitinib dose (between 5 and 25 mg BID) for ≥ 8 weeks prior to first dose of study treatment.		
7. Hæmoglobin < 11 g/dL (6.83 mmol/L).		
8. Absolute neutrophil count (ANC) ≥ 1.0 x 10e9/L.		
9. Part 1: Platelet counts ≥ 75 x 10e9/L.		
10. Part 2 and Part 3: Platelet counts ≥ 50 x 10e9/L.		
11. Part 2 and Part 3: Subjects who do not require packed red blood cells (PRBC) transfusion at screening and will not require any PRBC transfusions within 4 weeks prior to first dose of study treatment.		
12. Subjects must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted.		

Eksklusionskriterier:	Ja	Nej
1. Not able to understand and to comply with study instructions and requirements.		
2. Received any investigational agent for the treatment of MF (except ruxolitinib) within 30 days of first dose of study treatment or within 5 half-lives of the study treatment, whichever is greater.		
3. Received any investigational cancer vaccine or immunotherapy within 6 months prior to first dose of study treatment.		
4. Peripheral blood blasts count of > 10%.		
5. Inadequate liver function defined by any of these: Total bilirubin ≥ 2.5 x upper limit of normal (ULN) and subsequent determination of ≥ 2.5 x ULN; Alanine aminotransferase (ALT) > 2.5 x ULN; Aspartate aminotransferase (AST) > 2.5 x ULN.		
6. Severely impaired renal function defined by: Estimated creatinine clearance < 30mL/min.		
7. Active bacterial (including active and latent tuberculosis), fungal, parasitic, or viral infection that requires therapy.		
8. Known history of human immunodeficiency virus (HIV) infection or in the opinion of the investigator other clinically significant immunodeficiency syndromes such as X-linked agammaglobulinemia and common variable immune deficiency.		
9. Evidence of active HBV or HCV viral infection (HBsAg in the absence of HBsAb OR HCV Ab positive with HCV RNA positive). Subjects whose disease is controlled under antiviral therapy should not be excluded.		
10. History of progressive multifocal leuko-encephalopathy (PML).		
11. History of a second primary malignancy in the past 3 years in need of systemic treatment.		
12. History or current diagnosis of uncontrolled or significant cardiac disease including any of the following: • Myocardial infarction within the last 6 months • Uncontrolled congestive heart failure requiring treatment (New York Heart Association Grade ≥ 2), LVEF < 50% as determined by multigated acquisition (MUGA) scan or echocardiogram (ECHO), or uncontrolled hypertension defined by blood pressure ≥140 (systolic) /90 (diastolic) mmHg at rest (average of 3 consecutive readings) despite medical treatment • Unstable angina pectoris within the last 6 months		
13. History or current diagnosis of ECG abnormalities indicating significant risk of cardiac disease such as: • Resting QTcF ≥ 470 msec at pretreatment (baseline) for both male and female or impossibility to determine QTc		

Eksklusionskriterier:	Ja	Nej

• Concomitant clinically significant cardiac arrhythmias (e.g ventricular tachycardia), and clinically significant second or third-degree AV block without a pacemaker
• History of familial long QT syndrome or know family history of Torsade's de Pointe or any of the following:
  ○ Risk factors for Torsades de Pointe including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia
  ○ Inability to determine the QTcF interval		

14. Any condition which, in the opinion of the investigator, is likely to interfere with the successful collection of the measurements required for the study		
15. Contraindication or hypersensitivity to any drug or metabolites from similar class as study drug or to any excipients of the study drug formulation.		
16. Any other known disease that could compromise participation in the study including gastrointestinal (GI) disorders impacting absorption of ruxolitinib or siremadlin (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection), evidence of major active bleeding or history of bleeding diathesis or major coagulopathy.		
17. Received a monoclonal antibody or immunoglobulin-based agent within 1 year of screening or has documented severe hypersensitivity reactions/immunogenicity to a prior biologic.		
18. Significant immune deficiency (including chronic use of immunosuppressive drugs) in the opinion of the investigator.		
19. Pregnant females or females who have given birth within the past 90 days or who are breastfeeding.		
20. Women of child-bearing potential (WOCBP), defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 30 days after the last dose of single-agent ruxolitinib (control/monotherapy), for 30 days after the last dose of ruxolitinib or siremadlin for subjects on ruxolitinib + siremadlin (or siremadlin monotherapy), for 105 days after the last dose of crizanlizumab for subjects on ruxolitinib + crizanlizumab (or crizanlizumabmonotherapy), and for 150 days after the last dose of MBG453 for subjects on ruxolitinib+ MBG453 (or MBG453 monotherapy). Highly effective contraception methods include: • Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception • Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or bilateral tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the		

Eksklusionskriterier:	Ja	Nej
woman has been confirmed by follow-up hormone level assessment • Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject • Use of an intrauterine device (IUD) or intrauterine system (IUS). Any forms of hormonal contraception for example oral, injectable, implanted, transdermal hormonal patch or hormonal vaginal ring are excluded from use Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks prior to start of study treatment. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered not of child bearing potential If local regulations deviate from the contraception methods listed above (for women of child-bearing potential or male) to prevent pregnancy, local regulations apply and will be described in the ICF.		
21. Sexually active males unless they use a condom during intercourse while taking siremadlin and for 2 weeks after siremadlin discontinuation, and thus do not attempt to father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.		
22. History of drug-induced pneumonitis or current pneumonitis.		
23. Use of erythropoietin stimulating agents (ESA) ≤ 3 months prior to first dose of study treatment.		
24. Splenic irradiation within 6 months prior to the first dose of study drug.		
25. Received blood platelet transfusion within 28 days prior to first dose of study treatment.		
26. Subjects with known TP53 mutation or deletion of TP53.		
27. Currently receiving treatment with drug or herbal medications that meet any of the following criteria: • Require the use of herbal preparations/medications and dietary supplements (except for vitamins) within 7 days prior to first dose of study treatment or are expected to use such products during the entire study. • Receiving fluconazole at doses higher than 200 mg daily. • Require treatment with moderate or strong CYP3A4/5 inducers within 14 days prior to first dose of study treatment and cannot be discontinued or switched to alternative medication prior to first dose of study treatment.		

Eksklusionskriterier:	Ja	Nej
• Require treatment with strong CYP2C9 inducers within 14 days prior to first dose of study treatment and cannot be discontinued or switched to alternative medication prior to first dose of study treatment. • Require treatment with substrates of CYP3A4/5 inhibitors within 48 hours prior to first dose of study treatment and cannot be discontinued or switched to alternative medication prior to first dose of study treatment. • Require treatment with strong CYP2C9 inhibitors within 48 hours prior to first dose of study treatment and cannot be discontinued or switched to alternative medication prior to first dose of study treatment. • Require treatment with substrates of CYP3A4/5 with a narrow therapeutic index within 24 hours prior to first dose of study treatment. (NOTE: the above criteria are consolidated across ALL treatment arms to accommodate for subject randomization process. For 'treatment arm' specific restrictions related to concomitant medication while on 'study treatment', please refer to section 6.2.2 of the protocol.)		
28. Eligible for allogeneic hematopoietic stem cell transplantation (ASCT) at the time of enrollment.		
29. Use of live vaccines within 30 days prior to first dose of study treatment.		
30. Use of systemic steroid therapy and other immunosuppressive drugs within 14 days prior to first dose of study treatment (>10 mg/day prednisone or equivalent). Topical, inhaled, nasal, ophthalmic steroids are allowed. Replacement therapy, steroids given in the context of a transfusion are allowed and not considered a form of systemic treatment.		
31. Occurence of any clinically significant bleeding events within 6 months prior to first doseof study treatment.		
32. For patients treated with LTT462 in Part 1 and for all patients in Part 2 and Part 3 (if an LTT462 arm is included in the randomization for Part 2 or Part 3): Pre-existing retinal vein occlusion (RVO) or current risk factors (apart from the underlying MF) for RVO (e.g. uncontrolled glaucoma or ocular hypertension, history of hyperviscosity or hypercoagulability syndromes).		

Dato: ___/___ 20__Læge (underskrift): _____ Læge (init): _____