KURZPROTOKOLL
FREEDOM2

Öffentlicher Titel	Phase III Studie zu Fedratinib bei Fibrose und mittlerem oder hohem DIPSS-Risiko
Wissenschaftl. Titel	An Efficacy and Safety Study of Fedratinib Compared to Best Available Therapy in Subjects With DIPSS-intermediate or High-risk Primary Myelofibrosis, Post-polycythemia Vera Myelofibrosis, or Post-essential Thrombocythemia Myelofibrosis and Previously Treated With Ruxolitinib
Kurztitel	FREEDOM2
Studienart	multizentrisch, prospektiv, Therapiestudie, randomisiert, offen/unverblindet, zweiarmig
Studienphase	Phase III
Erkrankung	Blut: Myeloische Neoplasien/Dysplasien: Myeloproliferative Neoplasien (MPN)
Einschlusskriterien	- Subject is at least 18 years of age at the time of signing the informed consent form (ICF) - Subject has an Eastern Cooperative Oncology Group (ECOG) Performance Score (PS) of 0, 1 or 2 - Subject has diagnosis of primary myelofibrosis (PMF) according to the 2016 World Health Organization (WHO) criteria, or diagnosis of post-ET or post-PV myelofibrosis according to the IWG-MRT 2007 criteria, confirmed by the most recent local pathology report - Subject has a DIPSS Risk score of Intermediate-2 or High - Subject has a measurable splenomegaly during the screening period as demonstrated by spleen volume of >= 450 cm3 by MRI or CT-scan and by palpable spleen measuring >= 5 cm below the left costal margin - Subject has a measurable total symptoms score (>= 1) as measured by the Myelofibrosis Symptom Assessment Form (MFSAF) - Subject has been previously exposed to ruxolitinib, and must meet at least one of the following criteria (a and/or b) a. Treatment with ruxolitinib for >= 3 months with inadequate efficacy response (refractory) defined as < 10% spleen volume reduction by MRI or < 30% decrease from baseline in spleen size by palpation or regrowth (relapsed) to these parameters following an initial response b. Treatment with ruxolitinib for >= 28 days complicated by any of the following (intolerant): o Development of a red blood cell transfusion requirement (at least 2 units/month for 2 months) or o Grade >= 3 AEs of thrombocytopenia, anemia, hematoma, and/or hemorrhage while on treatment with ruxolitinib - Subject must have treatment-related toxicities from prior therapy resolved to Grade 1 or pretreatment baseline before start of last therapy prior to randomization - Subject must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted - Subject is willing and able to adhere to the study visit schedule and other protocol requirements - A female of childbearing potential (FCBP) must: Have 2 negative pregnancy tests as verified by the Investigator during screening prior to starting study treatment. She must agree to ongoing pregnancy testing during the course of the study, and after end of study treatment. This applies even if the subject practices true abstinence* from heterosexual contact. Either commit to true abstinence* from heterosexual contact (which must be reviewed on a monthly basis and source documented) or agree to use and be able to comply with highly effective contraception** without interruption, -14 days prior to starting investigational product, during the study treatment (including dose interruptions), and for 30 days after discontinuation of study treatment. Note: A female of childbearing potential (FCBP) is a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy, or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months)

- A male subject must: Practice true abstinence* (which must be reviewed on a monthly basis) or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 30 days following investigational product discontinuation, or longer if required for each compound and/or by local regulations, even if he has undergone a successful vasectomy

Ausschlusskriterien

- Any of the following laboratory abnormalities: Platelets < 50 x 109/L Absolute neutrophil count (ANC) < 1.0 x 109/L White blood count (WBC) > 100 x 109/L Myeloblasts >= 5 % in peripheral blood Estimated glomerular filtration rate < 30 mL/min/1.73 m2 (as per the Modification of Diet in Renal Disease [MDRD] formula) Serum amylase or lipase > 1.5 x upper limit of normal (ULN) Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 x upper limit of normal (ULN) Total bilirubin > 1.5 x ULN, subject's total bilirubin between 1.5 - 3.0 x ULN are eligible if the direct bilirubin fraction is < 25% of the total bilirubin
- Subject is pregnant or lactating female
- Subject with previous splenectomy
- Subject with previous or planned hematopoietic cell transplant
- Subject with prior history of Wernicke encephalopathy (WE)
- Subject with signs or symptoms of WE (eg, severe ataxia, ocular paralysis or cerebellar signs) without documented exclusion of WE by thiamine level and brain MRI
- Subject with thiamine deficiency, defined as thiamine levels in whole blood below normal range according to institutional standard and not demonstrated to be corrected prior to randomization
- Subject with concomitant treatment with or use of pharmaceutical, herbal agents or food known to be strong inducers of Cytochrome P450 3A4 (CYP3A4), sensitive CYP3A4 substrates with narrow therapeutic range, sensitive Cytochrome P450 2C19 (CYP2C19) substrates with narrow therapeutic range, or sensitive Cytochrome P450 2D6 (CYP2D6) substrates with narrow therapeutic range
- Subject on any chemotherapy, immunomodulatory drug therapy (eg, thalidomide, interferon-alpha), anagrelide, immunosuppressive therapy, systemic corticosteroids > 10 mg/day prednisone or equivalent. Subjects who have had prior exposure to hydroxyurea (eg, Hydrea) in the past may be enrolled into the study as long as it has not been administered within 14 days prior to randomization
- Subject has received ruxolitinib within 14 days prior to randomization
- Subject with previous exposure to Janus kinase (JAK) inhibitor(s) other than ruxolitinib treatment
- Subject on treatment with aspirin with doses > 150 mg daily
- Subject with major surgery within 28 days prior to randomization
- Subject with diagnosis of chronic liver disease (eg, chronic alcoholic liver disease, autoimmune hepatitis, sclerosing cholangitis, primary biliary cirrhosis, hemochromatosis, non-alcoholic steatohepatitis)
- Subject with prior malignancy other than the disease under study unless the subject has not required treatment for the malignancy for at least 3 years prior to randomization. However, subject with the following history/concurrent conditions provided successfully treated may enroll: non-invasive skin cancer, in situ cervical cancer, carcinoma in situ of the breast, incidental histologic finding of prostate cancer (T1a or T1b using the tumor, nodes, metastasis [TNM] clinical staging system), or is free of disease and on hormonal treatment only
- Subject with uncontrolled congestive heart failure (New York Heart Association Classification 3 or 4)

	- Subject with known human immunodeficiency virus (HIV), known active infectious Hepatitis B (HepB), and/or known active infectious Hepatitis C (HepC) - Subject with serious active infection - Subject with presence of any significant gastric or other disorder that would inhibit absorption of oral medication - Subject is unable to swallow capsule - Subject with any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study - Subject has any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study - Subject has any condition that confounds the ability to interpret data from the study - Subject with participation in any study of an investigational agent (drug, biologic, device) within 30 days prior to randomization - Subject with a life expectancy of less than 6 months
Alter	18 Jahre und älter
Prüfzentren	**Innere Medizin 2** (Geschlossen) Hämatologie / Medizinische Onkologie Theodor-Stern-Kai 7 60590 Frankfurt am Main Anja Binckebanck Tel: 069 6301-6221 Fax: 069 6301-7463 binckebanck@em.uni-frankfurt.de
Sponsor	Celgene GmbH
Registrierung in anderen Studienregistern	ClinicalTrials.gov NCT03952039 (primäres Register) EudraCT 2018-003411-21
Links	Studiendokumente zum Download (roXtra)