88549968MPN1001

Étude de première administration chez l'homme évaluant la sécurité, la pharmacocinétique et la pharmacodynamique du JNJ-88549968, un anticorps bispécifique de redirection des lymphocytes T dans le traitement des néoplasies myéloprolifératives NMP porteuses de mutations du gène CALR.

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https://classic.clinicaltrials.gov/ct2/show/NCT06150157

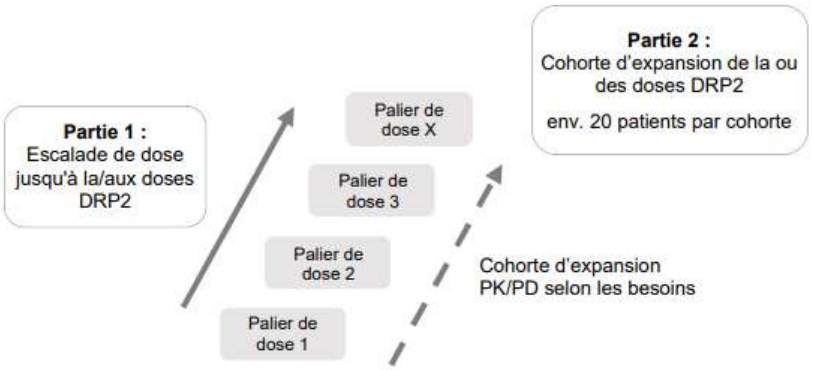
Population cible :

Il s'agit d'une étude de première administration chez l'homme, réalisée en ouvert, visant à caractériser la sécurité d'emploi et à déterminer la ou les doses DRP2 putatives ainsi que le ou les schémas posologiques optimaux du JNJ-88549968 chez des patients âgés de ≥ 18 ans atteints de néoplasies myéloprolifératives (NMP) et porteurs de mutation CALRmut diagnostiqués comme thrombocytémie essentielle ou myélofibrose

Traitement à l'étude :

Le JNJ-88549968 est un anticorps bispécifique de redirection des lymphocytes T, qui reconnaît l'antigène CD3 sur les lymphocytes T et la mutation de la calréticuline (CALRm) sur un clone de NMP. Le mécanisme d'action du JNJ-88549968 est d'agir comme un pont entre les cellules cancéreuses du NMP et les lymphocytes T cytotoxiques (LTC).

Schéma de traitement :



Abréviations : PD = pharmacodynamique ; PK = pharmacocinétique ; DRP2 = dose recommandée en phase II.

Rythme des visites :

L'étude commencera par une dose qui n'est pas ajustée au poids (« dose fixe ») et avec une injection SC pour la voie d'administration. L'escalade de dose commencera à une dose initiale de 0,6 mg en SC administrée tous les 21 jours. Sur la base de l'examen du SET des données apparues sous traitement, d'autres schémas posologiques (p. ex. un intervalle de 2 semaines) pourront être envisagés. La ou les escalades de dose pourront être mises en place selon leur propre calendrier pour atteindre la dose cible.

RÉFÉRENCE DANS LE PROTOCOLE		SÉLECTION	TRAITEMENT					POST-TRAITEMENT
			Escalade de dose et première dose cible			Doses cible	Fin du traitement	
	ÉVALUATION OU PROCÉDURE	≤ 30 jours avant la première dose	Administration du jour 1	+24h (± 2h)	+48h (± 2h)	± 48h	30 (± 14) jours après la dernière dose	60 (± 14) jours après la dernière dose
	Visite au centre	X	X	X	X	X	X	X

Critères d'inclusion	Y	N
1. Be ≥18 years of age (or the legal age of majority in the jurisdiction in which the study is taking place, whichever the greater) at the time of informed consent.		
2. Have a diagnosis of either ET or MF as defined by the 2022 WHO criteria (WHO Classification of Tumours Editorial Board 2022) that meets the stated risk criteria: **Essential Thrombocythemia** - High-risk of thrombosis or hemorrhage, defined as any 1 of the following: - Age >60 years - Platelet count >1500 x 109 /L at any point during the participant's disease - Previous documented thrombosis (including transient ischemic attack [TIA]), erythromelalgia, or migraine (severe, recurrent, requiring medications, and felt to be secondary to the MPN) either after diagnosis or within 10 years before diagnosis and considered to be disease-related. - Previous hemorrhage related to ET - Diabetes mellitus or hypertension requiring pharmacological therapy >6 months **AND** Intolerant or resistant or refractory to hydroxyrurea (HU), defined as any 1 of the following according to NCCN Guidelines Version 1.2023: -Platelet count >600 x 10^9 /L after 3 months of at least 2 g/day or maximum tolerated dose (MTD) of HU (2.5 g/day in participants with a body weight >80 kg) -Platelet count >400 x 10^9/L and WBC <2.5 x 10^9/L at any dose of HU (for a period of at least 3 months) -Platelet count >400 x 10^9/L and hemoglobulin <10 g/dL at any dose of HU(for a period of at least 3 months) -Presence of leg ulcers or other unacceptable mucocutaneous manifestations at any dose of HU -HU-related fever **Myelofibrosis (primary or post-ET)** **Primary Myelofibrosis** : Dynamic International Prognostic Scoring System (DIPSS; Table 25; Passamonti 2010) Intermediate 1-2 or High-Risk with a blast percentage not consistently exceeding 20% in blood or bone marrow **Post-ET MF :** MYSEC-PM (Table 26; Passamonti 2017) Intermediate 1-2 or High-Risk with a blast percentage not consistently exceeding 20% in blood or bone marrow **AND** **Ineligible or intolerant orresistant / refractory to JAKi therapy** Ineligible		

JAKi contraindicated due to prior history of severe infections such as tuberculosis, progressive multifocal leukoencephalopathy, and skin malignancies that are known to be associated or exacerbated by JAKi, or other significant considerations as documented by the treating physician. <u>Intolerant</u> a) Hematologic toxicity - platelet count <50 × 109/L and/or neutrophils ≤0.5 × 109/L despite recommended dose adjustments and interruptions; **<u>or</u>** b) ≥Grade 3 nonhematologic toxicity as per the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, 2017 <u>Resistant / Refractory</u> Evidence would include: a)persistent splenomegaly or b) lack of symptom improvement or c) persistent leukoerythroblastosis or d) anemia <10g/dL or e) leukocytosis >11x10^9 /L		
3. Positive for a CALR driver mutation of ET or MF		
4. Have received prior therapy(ies): **<u>Essential Thrombocythemia</u>** At least 2 lines of prior cytoreductive therapy, at least 1 of which must have been HU. **<u>Myelofibrosis</u>** At least 1 prior JAK inhibitor (JAKi) therapy unless ineligible as described in Criterion 2		
5. Have discontinued concurrent use of the following therapies: **<u>Essential Thrombocythemia</u>** Interferon-α (pegylated or standard preparation), anagrelide, busulfan. Exception: HU is permitted.		

Myelofibrosis JAKi, immunomodulatory drug therapy (such as thalidomide), danazol, or other therapy intended to lead to disease modification		
6. Criterion modified per Amendment EEA-1: 6.1 Have an ECOG performance status grade of 0 or 1		
7. Have the following clinical hematology laboratory values predose: a. Hemoglobin ≥8.0 g/dL b. Neutrophils ≥0.75 x 10^9 /L without the assistance of granulocyte growth factors within 4 weeks of the first dose of study drug c. Platelets ≥50 x 10^9 /L without the assistance of thrombopoietic factors or transfusions		
8. Participants should have the following clinical chemistry laboratory values predose: a. ALT: ≤3 x ULN b. AST: ≤3 x ULN c. Direct bilirubin: ≤1.5 x ULN d. Renal function: Estimated or measured glomerular filtration rate ≥40 mL/min per MDRD formula (See Appendix 9.)		
9. Known HIV-positive participants are eligible if they meet all of the following: a. No detectable viral load (ie, 300 cells/mm3 at screening b. CD4+ count >300 cells/mm3 at screening c. No AIDS-defining opportunistic infection within 6 months of screening d. Receiving highly active antiretroviral therapy (HAART). Any changes in HAART due to resistance/progression should occur at least 3 months prior to screening. A change in HAART due to toxicity is allowed up to 4 weeks prior to screening. **Note**: HAART that could interfere with study treatment is excluded (consult the sponsor for a review of medications prior to enrollment).		
10. A participant of childbearing potential must have a negative highly sensitive serum (eg, beta-human chorionic gonadotropin [β-hCG]) pregnancy test at screening and within 72 hours of the first dose of study treatment and must agree to further serum or urine pregnancy tests during the study.		
11. A participant ofchildbearing potential must practice at least 1 highly effective method of contraception (details in Appendix 5) throughout the study and at least 90 days after the last dose of study treatment. Note: If the participant becomes of childbearing potential after the start of the study, the participant must comply with this criterion.		
12. A participant using oral contraceptives must use an additional barrier contraceptive method (details in Appendix 5).		

13. A participant must agree not to be pregnant, breastfeeding, or planning to become pregnant while enrolled in this study or within 90 days after the last dose of study treatment.		
14. A participant must agree not to donate gametes (ie, eggs or sperm) or freeze for future use for the purposes of assisted reproduction during the study and for a period of 6 months after receiving the last dose ofstudy treatment. Participants should consider preservation of gametes prior to study treatment as anticancer treatments may impair fertility.		
15. A participant must wear a condom when engaging in any activity that allows for passage of ejaculate to another person during the study and for at least 90 days after receiving the last dose of study treatment. If a participant's partner is of childbearing potential, the participant must use condoms (with or without spermicide) and the partner must also be practicing a highly effective method of contraception (see Appendix 5). A vasectomized male participant must still use a condom (with or without spermicide), but the partner is not required to use contraception		
16. A participant must agree not to plan to father a child while enrolled in this study or within 3 months after the last dose of study treatment.		
17. Must sign an ICF indicating that the participant understands the purpose of, and procedures required for, the study and is willing to participate in the study.		
18. Be willing and able to adhere to the lifestyle restrictions specified in this protocol		

Critères d'exclusion	**Y**	**N**
1. Known allergies, hypersensitivity, or intolerance to the excipients of the study treatment.		
2. Chemotherapy, cytoreductive therapy, targeted therapy, or immunotherapy at 5 half-lives or 2 weeks, whichever is shorter, prior to the planned first dose of study treatment. EXCEPTIONS: a. HU is permitted on study b. JAK inhibitor withdrawal to be tapered with 1 week washout as per Section 6.8.4.1		
3. Criterion modified per EEA-1: 3.1 Any prior treatment with CALRmut-targeted therapy		
4. Concurrent or recently diagnosed or treated malignancies present at the time of participant screening. Exceptions are squamous and basal cell carcinoma of the skin, carcinoma in situ of the cervix, and any malignancy that is considered cured or has minimal risk of recurrence within 1 year of first dose of study treatment in the opinion of both the investigator and sponsor's medical monitor. Participants cured of another malignant disease with no sign of relapse ≥3 years after treatment ended are allowed to enter the study		

5. Prior solid organ transplantation.		
6. Either of the following regarding hematopoietic stem cell transplantation: a. Prior treatment with allogenic stem cell transplant ≤6 months before the first dose of JNJ88549968 or b. Evidence of graft versus host disease (GVHD) that requires immunosuppressant therapy		
7. Active autoimmune disease that requires systemic immunosuppressive medications (eg, chronic corticosteroid, methotrexate, or tacrolimus)		
8. Toxicities from previous anticancer therapies that have not resolved to baseline levels, or to Grade 1 or less, or to Grade ≤2 for alopecia, peripheral neuropathy, and vitiligo.		
9. History of clinically significant cardiovascular disease within 6 months prior to the first dose of study treatment including, but not limited to: a. Myocardial infarction b. Severe or unstable angina c. Clinically significant ventricular arrhythmias or unexplained syncope, not believed to be vasovagal in nature or due to dehydration d. History of severe non-ischemic cardiomyopathy e. Congestive heart failure (New York Heart Association class III-IV) f. Uncontrolled (persistent) hypertension: systolic blood pressure >159 mm Hg OR diastolic blood pressure >99 mm Hg g. Stroke or transient ischemic attack h. Pericarditis or clinically significant pericardial effusion i. Myocarditis j. Endocarditis k. Acute ischemic limb		
10. Clinically significant pulmonary compromise, particularly the need for supplemental oxygen use to maintain adequate oxygenation..		
11. Criterion modified per EEA-1: 11.1 Evidence of active viral (including chronic EBV), bacterial, or uncontrolled systemic fungal infection requiring systemic treatment within 14 days before the first dose of study treatment		
12. Fever (body temperature ≥38.0°C/100.4°F)in the 48 hrs prior to first dose of study treatment		
13. Trauma or major surgery (eg, requiring general anesthesia) within 28 days prior to the first dose of study treatment. Note: Participants with planned surgical procedures to be conducted under local anesthesia may participate		
14. Any serious underlying medical or psychiatric condition (eg, alcohol or drug abuse), dementia or altered mental status; or any issue that would impair the ability of the participant		

to receive or tolerate the planned treatment at the investigational site, to understand informed consent, or that in the opinion of the investigator would contraindicate the participation in the study or confound the protocol-specified assessments or results of the study.		
15. A prohibited medication that cannot be discontinued or substituted, or temporally interrupted during the study. Prohibited therapies are described in Section 6.8.4.		
16. Vaccination with a live, attenuated vaccine within 4 weeks before the first administration of study treatment.		
17. Body weight is <40 kg at screening and/or at the time of their first administration of study treatment		
18. Active infective hepatitis: -Seropositive for hepatitis B: defined by a positive test for hepatitis B surface antigen (HBsAg). Participants with resolved infection (ie, participants who are HbsAg negative with antibodies to total hepatitis B core antigen [anti-HBc] with or without the presence of hepatitis B surface antibody [anti-HBs]) must be screened using real-time polymerase chain reaction (RT-PCR) measurement of hepatitis B virus (HBV) DNA levels. Those who are RT-PCR positive will be excluded. Participants with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA by RT-PCR. (See Appendix 11.) -Known hepatitis C infection or positive serologic testing for hepatitis C virus (anti-HCV antibody). Positive hepatitis C antibody test result at screening or within 3 months prior to starting study treatment. NOTE: Participants with positive hepatitis C antibody due to prior resolved disease can be enrolled only if a confirmatory negative hepatitis C RNA test is obtained. Positive hepatitis C RNA test result at screening or within 3 months prior to first dose of study treatment. NOTE: Test is optional and participants with negative hepatitis C antibody test are not required to also undergo hepatitis C RNA testing. -Other known clinically active liver disease of infectious origin.		
19. Criterion added per Amendment EEA-1: History of pneumonitis or interstitial lung disease		
20. Criterion added per Amendment EEA-1: Those without evidence of stable anticoagulant therapy, defined as ≥4 weeks of unmodified anticoagulant therapy prior to the first administration of study treatment.		
21. Criterion added per Amendment EEA-1: History of Hemophagocytic Lymphohistiocytosis (HLH)/Macrophage Activation Syndrome (MAS)		