CGFL Centre Georges François Leclerc Ensemble, dépassons le cancer	**CRITERES DE SELECTION** **ETUDE GUIDE 2 REPAIR**	Identité patient (coller étiquette patient)
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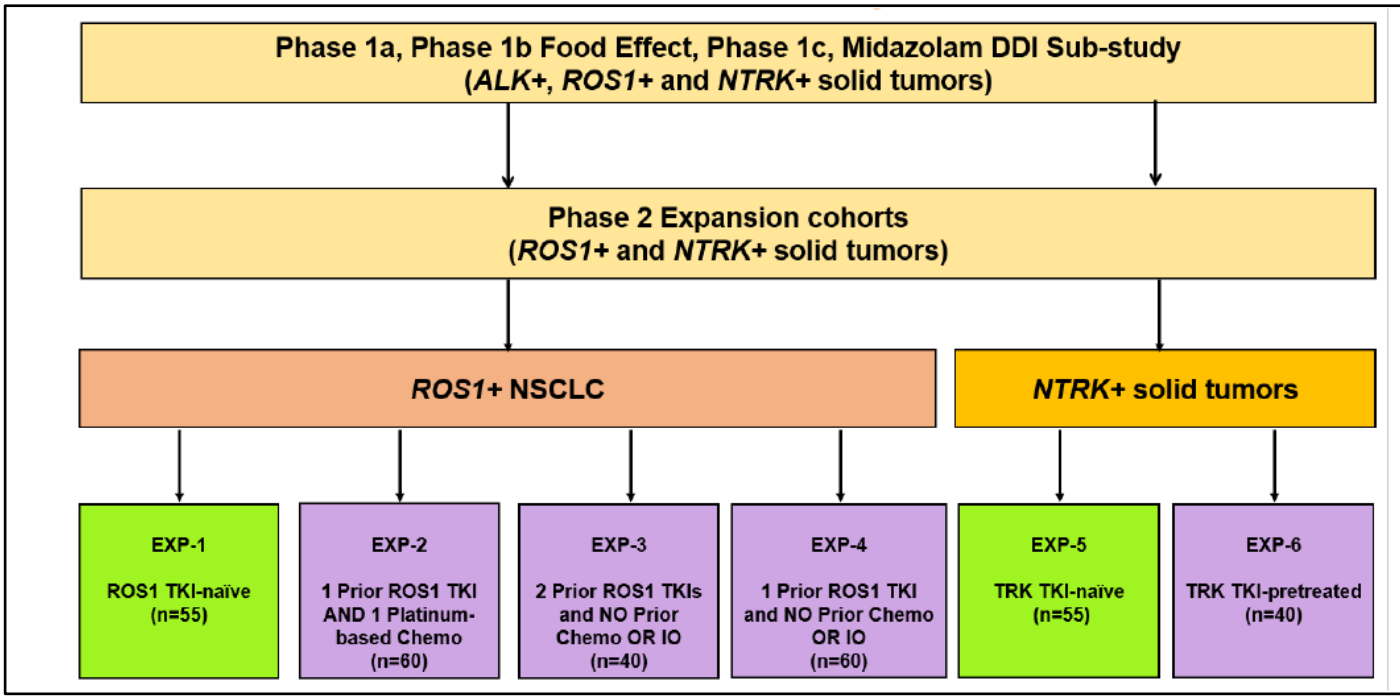
« TPX-0005-01 – TRIDENT »

Étude multicentrique, en ouvert, de Phase 1/2, menée pour la première fois chez l'homme évaluant la sécurité, la tolérance, la pharmacocinétique et l'activité antitumorale de TPX-0005 chez des patients présentant des tumeurs solides avancées porteuses de réarrangements du gène *ALK*, *ROS1* ou *NTRK1-3* (TRIDENT-1)



VALIDATION DES CRITERES DE SELECTION

Critères d'inclusion phase 1 :

Histologically or cytologically confirmed diagnosis of locally advanced or metastatic solid tumor (including primary CNS tumors; Stage IV, American Joint Committee on Cancer v.7) that harbors an *ALK, ROS1, NTRK1, NTRK2,* or *NTRK3* gene rearrangement as by: • All diagnostic tests must be conducted in CLIA lab or equivalent. • Any nucleic acid-based diagnostic testing method (e.g., next-generation sequencing [NGS], Sanger sequencing, reverse transcription-polymerase chain reaction) performed at a local clinical laboratory improvement amendments-certified (CLIA certified) or equivalently accredited diagnostic laboratory. In NGS test results, the fusion gene partner for *ALK, ROS1, NTRK1, NTRK2,* or *NTRK3* gene rearrangement has to be identified and reported. All tests must have been performed according to the product's instructions for use (IFU).	□ oui □ non

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• Break-apart fluorescence *in situ* hybridization (FISH) is allowed for diagnosis of *ALK*, *ROS1*, *NTRK1*, *NTRK2*, and *NTRK3* rearrangements. For *ALK* rearrangement detection in NSCLC, the FISH test has to be performed using the FDA-approved Abbott Molecular's Vysis® ALK Break-apart FISH Probe Kit. All tests must have been performed according to the product's IFU. • Immunohistochemistry (IHC) detection of *ROS1*, *NTRK1*, *NTRK2*, and *NTRK3* rearrangement will not directly qualify subjects. Archival tumor samples of these IHC-positive subjects (ROS1, TRKA, TRKB, TRKC) will have to be sent to the Turning Point Therapeutics' designated central laboratory for confirmation of *ROS1*, *NTRK1*, *NTRK2*, and *NTRK3* rearrangement prior to enrollment onto the trial. IHC detection of *ALK* rearrangement in NSCLC is allowed if performed using the Ventana ALK (D5F3) companion diagnostic assay. All tests must have been performed according to the product's IFU. • For subjects enrolled per the diagnostic tests outlined above and approved by Turning Point Therapeutics, central laboratory confirmation of the specific gene alteration is not required before start of repotrectinib treatment as long as adequate archival tissue is sent to the Turning Point Therapeutics' designated central laboratory.	
All subjects must have archival tissue sample or *de novo* tissue sample available and/or collected prior to enrollment. Formalin-fixed paraffin-embedded (FFPE) tissue block(s) from initial diagnosis that contain sufficient tissue to generate at least 10 (preferably 15), 5-micron thick unstained slides will be collected. If no FFPE block is available, then at least 10 (preferably 15) unbaked, 5-micron thick unstained slides with a minimum of 20% (preferably 25%) tumor content and 1 Hematoxylin and eosin stain (H&E) slide must be provided. Specimens will be sent to the Turning Point Therapeutics-designated central laboratories for *ALK*, *ROS1*, or *NTRK* rearrangement status confirmation.	□ oui □ non
ECOG PS 0–1	□ oui □ non
Age ≥18 (or age ≥ 20 of age as required by local regulation).	□ oui □ non
Willing and able to provide written institutional review board (IRB)/institutional ethics committee-approved Informed Consent.	□ oui □ non
At least 1 measurable target lesion according to RECIST version 1.1. CNS-only measurable disease as defined by RECIST version 1.1 is allowed.	□ oui □ non
Prior cytotoxic chemotherapy for advanced or metastatic disease is allowed. At the time of starting treatment with repotrectinib, at least 14 days or 5 half-lives (whichever is shorter) must have elapsed after discontinuation of prior cytotoxic chemotherapy (or at least 42 days for prior nitrosoureas, mitomycin C, and liposomal doxorubicin) and all side effects from prior treatments must have resolved to grade ≤ 1 (CTCAE Version 4.03) with the exception of alopecia.	□ oui □ non
Prior immunotherapy (e.g., anti-PD-1, anti-PDL1, anti-TIM3, anti-OX40) is allowed (except for the treatment-naïve expansion cohort). At the time of starting treatment with repotrectinib, at least 14 days must have elapsed after discontinuation of prior immunotherapy treatment and all immune-related side effects from prior treatments must have resolved to grade ≤ 1.	□ oui □ non

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Subjects with advanced solid tumors harboring *ALK*, *ROS1*, *NTRK1*, *NTRK2*, or *NTRK3* rearrangements are eligible. There is no limit to the number of prior chemotherapies, immunotherapy, or TKI regimens.	□ oui □ non
At least 7 days or 5 half-lives (whichever is shorter) must have elapsed since completion of treatment with the last ALKi, ROS1i, or TRKi prior to starting treatment with repotrectinib for subjects enrolling into the TKI-pretreated expansion cohorts. In the midazolam DDI sub-study, if a subject received prior treatment of a TKI that is a moderate/strong inducer or inhibitor of CYP3A, such as lorlatinib, the required wash-out period will be at least 14 days to allow complete wash out of its induction or inhibition effects. All side effects from prior treatments with ALKi, ROS1i, or TRKi must have resolved to grade ≤ 1 prior to starting treatment with repotrectinib; however, the most immediate treatment prior to enrollment does not have to be a TKI. • Prior ALKi allowed include crizotinib, ceritinib, alectinib, brigatinib, lorlatinib, ensartinib and entrectinib • Prior ROS1i allowed include crizotinib, ceritinib, lorlatinib, brigatinib, entrectinib, ensartinib, DS6051b, cabozantinib • Prior TRKi allowed include entrectinib, larotrectinib, LOXO-195, DS6051b • Other prior ALKi, ROS1i, and TRKi not listed above may be allowed after discussion with Turning Point Therapeutics	□ oui □ non
Subjects with asymptomatic CNS metastases (treated or untreated) and/or asymptomatic leptomeningeal carcinomatosis are eligible to enroll if they satisfy the following criteria: • Subjects requiring steroids at a stable or decreasing dose (≤ 12 mg/day dexamethasone or equivalent) for at least 14 days are eligible. Subjects on stable doses of levetiracetam (same dose for 14 days) are eligible to be enrolled. •A minimum of 14 days must have elapsed from the completion of whole brain radiation treatment (WBRT) before the start of treatment with repotrectinib, and all side effects (with the exception of alopecia) from WBRT are resolved to CTCAE grade ≤ 1. • A minimum of 7 days must have elapsed from the completion of stereotactic radiosurgery before the start of treatment with repotrectinib, and all side effects (with the exception of alopecia) from stereotactic radiosurgery are resolved to CTCAE grade ≤ 1.	□ oui □ non
Baseline laboratory values fulfilling the following requirements:	□ oui □ non
Females of childbearing potential must have a negative serum pregnancy test during screening and be neither breast feeding nor intending to become pregnant during study participation. Females of childbearing potential must agree to avoid pregnancy during the study and agree to the use of 2 effective contraceptive methods (hormonal or barrier method of birth control, or abstinence) prior to study entry, for the duration of study participation, and in the following 90 days after discontinuation of study treatment (see Section 6.4.4. Men with partner(s) of childbearing potential must take appropriate precautions to avoid fathering a child from screening until 28 days after discontinuation of study treatment and to use appropriate barrier contraception or abstinence.	

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Capability to swallow capsules intact (without chewing, crushing, or opening).	□ oui □ non
Life expectancy ≥3 months.	□ oui □ non□ oui □ non
Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.	

Critères d'inclusion phase 2 :

. Histologically or cytologically confirmed diagnosis of locally advanced, or metastatic solid tumor (including primary CNS tumors) that harbors a ROS1or NTRK1-3 gene fusion. Note: Locally advanced disease is defined as Stage III when patient is not a candidate for surgery, radiation, or multi-modality therapy and metastatic disease is defined as Stage IV per the American Joint Committee on Cancer Eighth Edition Cancer Staging Manual guidelines (Rami-Porta 2017).	□ oui □ non
Subject must have a documented *ROS1* or *NTRK1-3* gene fusion determined by tissue-based local testing using either: a) a next-generation sequencing (NGS) or quantitative polymerase chain reaction (qPCR) test will be accepted to determine molecular eligibility. □ □Adequate tumor tissue needs to be sent to the Sponsor designated central diagnostic laboratory for retrospective confirmation by a central diagnostic laboratory test selected by the Sponsor. In cases where archived tumor tissue is not available, a de novo biopsy should be obtained at Screening or as soon as possible after enrollment. See the Study Laboratory Manual for details. • If NGS was used, the partner of the fusion target gene needs to be identified. • Retrospective confirmation by a central diagnostic laboratory test selected by the Sponsor is not required if ROS1 or NTRK1-3 gene fusion were determined by the Repotrectinib clinical trial assay (CTA). OR b) a fluorescence in situ hybridization (FISH) test AND prospective confirmation of fusion status by a central diagnostic laboratory test selected by the Sponsor PRIOR to enrollment will be accepted to determine molecular eligibility. • Adequate tumor tissue must be sent to the Sponsor designated central diagnostic laboratory for prospective confirmation by a central diagnostic laboratory test selected by the Sponsor	□ oui □ non

PRIOR to enrollment. In cases where archived tumor tissue is not available, a de novo biopsy should be obtained for this purpose. See the Study Laboratory Manual for details. a) All tests need to be performed in a Clinical Laboratory Improvement Amendments (CLIA) laboratory or equivalently accredited diagnostic laboratory.	
Eastern Cooperative Oncology Group (ECOG) Performance Status 0–1. Note: Subjects who are unable to walk because of paralysis or tumor pain, but who are in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score	□ oui □ non
Age ≥18 (or age ≥ 20 as required by local regulation).	□ oui □ non
Willing and able to provide written institutional review board (IRB)/institutional ethics committee-approved Informed Consent.	□ oui □ non
At least 1 measurable target lesion according to RECIST (v1.1) **prospectively** confirmed by Blinded Independent Central Radiology Review (BICR), selected by Sponsor, PRIOR to enrollment. Subjects with CNS-only measurable disease ≥10 mm as defined by RECIST (v1.1) are eligible.	□ oui □ non
Subjects with advanced solid tumors harboring ROS1, NTRK1, NTRK2, or NTRK3 rearrangement will be assigned into 6 distinct expansion (EXP) cohorts provided all inclusion and exclusion criteria are met. • **EXP-1: ROS1 TKI-naïve *ROS1*+ NSCLC (n=55)**. • No prior exposure to ROS1 TKI is allowed. • Up to one prior line of chemotherapy OR immunotherapy is allowed (chemo- or immunotherapy-based combination regimen is considered as one line of treatment). **EXP-2: 1 Prior ROS1 TKI AND 1 Platinum-based Chemotherapy/Immunotherapy *ROS1*+ NSCLC (n=60).** isease progressionor intolerant to one prior line of ROS1 TKI. OS1 TKIs used in a prior line of treatment are limited to crizotinib, ceritinib, entrectinib, or lorlatinib. Note: Any previous exposure to a ROS1 TKI is considered as one prior line of TKI treatment (e.g., if the same ROS1 TKI was given before and after a chemotherapy or other systemic therapy, it is considered as 2 prior TKIs and the subject would not be eligible for EXP-2). addition, the subject must have received one prior line of platinum-based chemotherapy OR one prior line of platinum-based chemotherapy in combination with immunotherapy before or after a ROS1 TKI (Note: subject is not eligible if he/she has been treated with more than one line of chemotherapy OR has received immunotherapy alone).	□ oui □ non

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XP-3: 2 Prior ROS1 TKIs and NO Chemotherapy or Immunotherapy *ROS1*+ NSCLC (n=40). isease progression or intolerant to 2 prior lines of a ROS1 TKI treatment. OS1 TKI used in prior lines of treatment are limited to crizotinib, ceritinib, entrectinib, lorlatinib, brigatinib, ensartinib, or cabozantinib. Other prior ROS1TKI agents that are not listed may be allowed after discussion with the Sponsor Medical Monitor. Note: Any previous exposure to a ROS1 TKI is considered as one prior line of TKI treatment (e.g., if 2 different ROS1 TKIs are utilized, or the same ROS1 TKI was given before and after a chemotherapy or other systemic therapy, it is considered as 2 prior TKIs and the subject would be eligible). o prior lines of chemotherapy or immunotherapy are allowed. **XP-4: 1 Prior ROS1 TKI and NO Chemotherapy or Immunotherapy *ROS1*+ NSCLC (n=60)**. isease progression or intolerant to one prior line of a ROS1 TKI. OS1 TKIs used in a prior line of treatment are limited to crizotinib, ceritinib, entrectinib, or lorlatinib. Note: Any previous exposure to a ROS1 TKI is considered as one prior line of TKI treatment (e.g., if the same ROS1 TKI was given before and after a chemotherapy or other systemic therapy, it is considered as 2 prior TKIs and the subject would not be eligible for EXP-4). Note: No prior lines of chemotherapy or immunotherapy are allowed • **EXP-5: TRK TKI-naïve NTRK+ solid tumors (n=55)**. • No prior TRK TKI is allowed. • Prior lines on chemotherapy or immunotherapy are allowed. Disease progression on prior systemic therapy is required unless no appropriate therapeutic alternative exists. **EXP-6: TRK TKI-pretreated NTRK+ solid tumors (n=40)**: • Disease progressionor intolerant to 1 or 2 prior TRK TKIs only. • TRK TKI used in prior lines or treatment are limited to entrectinib, larotrectinib, or LOXO-195. Other prior TRKi not listed above may be allowed after discussion with the Sponsor Medical Monitor. Note: Any previous exposure of a TRK TKI is considered as one prior line of TKI treatment, e.g. if 2 different TRK TKIs are utilized or the same TRK TKI was used before and after a chemo- or other systemic therapy, it is considered as 2 prior TKIs and the patient would be eligible. • Any prior lines on chemo or immunotherapy allowed.	
Required wash-out time that is related to prior therapies before starting repotrectinib treatment: • If the immediate prior treatment was a ROS1 or TRK TKI: Approximately 5 half-lives must have elapsed since completion of treatment with the last TKI for subjects enrolling into the pretreated expansion cohorts (EXP-2, -3, -4, and -6). All side effects from prior treatments with	□ oui □ non

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ROS1 or TRK TKI must have resolved to grade ≤1 prior to starting treatment with repotrectinib. • Approximately 5 half-lives must have elapsed after discontinuation of prior systemic chemotherapy (or at least 42 days for prior nitrosoureas and mitomycin C) and all side effects from prior treatments must have resolved to grade ≤1 with the exception of alopecia. • Approximately 5 half-lives must have elapsed after discontinuation of prior immunotherapy and all immune-related side effects from prior immunotherapy must have resolved to grade ≤1.	
Subjects with asymptomatic CNS metastases (treated or untreated) and/or asymptomatic leptomeningeal carcinomatosis are eligible to enroll if they satisfy the following criteria: • Subjects requiring steroids at a stable or decreasing dose (≤ 12 mg/day dexamethasone or equivalent) for at least 14 days are eligible. • Subjects on stable doses of levetiracetam (same dose for 14 days). • A minimum of 14 days must have elapsed from the completion of whole brain radiation treatment (WBRT) before the start of treatment with repotrectinib, and all side effects (with the exception of alopecia) from WBRT are resolved to grade ≤ 1. • A minimum of 7 days must have elapsed from the completion of stereotactic radiosurgery before the start of treatment with repotrectinib, and all side effects (with the exception of alopecia) from stereotactic radiosurgery are resolved to grade ≤ 1.	□ oui □ non

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Baseline laboratory values fulfilling the following requirements: □ oui □ non

Absolute Neutrophils Count (ANC)	≥1,500/mm^3 (1.5 x 10^9/L)
Platelets (PLT)	≥100,000/mm^3 (100 x 10^9/L) independent of t transfusion support for at least 7 days prior to
Hemoglobin	≥ 9.0 g/dL independent of transfusion support least 7 days prior to dosing
Creatinine Clearance*	> 40 mL/min
Total Serum Bilirubin	<1.5 x ULN
Liver Transaminases (AST/ALT)	<2.5 x ULN; < 5 x ULN if liver metastases ar present
Alkaline Phosphatase (ALP)	<2.5 x ULN; < 5 x ULN if liver and/or bone metastasis are present
Serum calcium, magnesium, phosphate, and potassium	Normal or CTCAE grade ≤1 with or without supplementation

AST/ALT = aspartate aminotransferase/alanine aminotransferase, ULN = upper limit of normal

* calculated by Cockcroft and Gault's formula: (140 - age [yr]) x body weight [Kg] x 1.23 x (0.85 if female) / serun creatinine [µmol/L].

Women of childbearing potential (WOCBP) must have a negative serum pregnancy test during screening and be neither breastfeeding nor intending to become pregnant during study participation. Female patients will be considered to be of childbearing potential unless they have undergone permanent sterilization or are postmenopausal. Postmenopausal is defined as at least 12 months without menses with no other medical reasons (e.g., chemical menopause due to anticancer treatment). For WOCBP and for male subjects with pregnant or nonpregnant WOCBP partners, agreement must be made to use highly effective contraceptive methods from the time of screening throughout the study until 3 months (WOCBP) or 6 months (men) after administration of the last dose of any study medication. Highly effective contraceptive methods consist of prior sterilization, intra-uterine device (IUD), intrauterine hormone-releasing system (IUS), injectable or implantable contraceptives. All males (study subjects and partners of female subjects) must agree to use condoms throughout the study and 6 months after administration of the last dose. True abstinence is acceptable if evaluated as consistent with the preferred and the usual lifestyle of the subject. Periodic abstinence is not an acceptable method of contraception. □ oui □ non

Ability to swallow capsules intact (without chewing, crushing, or opening). □ oui □ non

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Life expectancy ≥ 3 months.	□ oui □ non
Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.	□ oui □ non

Critères de non inclusion phase 1 et 2 :

Concurrent participation in another therapeutic clinical trial.	□ oui □ non
Symptomatic brain metastases or leptomeningeal involvement	□ oui □ non
History of previous cancer, except for squamous cell or basal-cell carcinoma of the skin, or any *in situ* carcinoma that has been completely resected, requiring therapy within the previous 2 years	□ oui □ non
Major surgery within 4 weeks of start of repotrectinib treatment. Radiation therapy (except palliative to relieve bone pain) within 2 weeks of study entry. Palliative radiation (≤10 fractions) must have been completed at least 48 hours prior to study entry.	□ oui □ non
Clinically significant cardiovascular disease (either active or within 6 months prior to enrollment): myocardial infarction, unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure (New York Heart Association Classification Class ≥ II), cerebrovascular accident or transient ischemic attack, symptomatic bradycardia, requirement for anti-arrhythmic medication. Ongoing cardiac dysrhythmias of CTCAE grade ≥2.	□ oui □ non
Any of the following cardiac criteria: • Mean resting corrected QT interval (ECG interval measured from the onset of the QRS complex to the end of the T wave) for heart rate (QTcF) > 470 msec obtained from 3 ECGs, using the screening clinic ECG machine-derived QTc value • Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG (e.g., complete left bundle branch block, third degree heart block, second degree heart block, PR interval > 250 msec) • Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalemia, congenital long QT syndrome, family history of long QT syndrome, or any concomitant medication known to prolong the QT interval	□ oui □ non

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Known active infections requiring ongoing treatment (bacterial, fungal, viral including human immunodeficiency virus positivity).	□ oui □ non
Gastrointestinal disease (e.g., Crohn's disease, ulcerative colitis, short gut syndrome) or other malabsorption syndromes that would impact on drug absorption.	□ oui □ non
Peripheral neuropathy, paresthesia, dizziness, dysgeusia, muscle weakness, ataxia grade ≥2.	□ oui □ non
History of extensive, disseminated, bilateral, or presence of CTCAE grade 3 or 4 interstitial fibrosis or interstitial lung disease including a history of pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, and pulmonary fibrosis. Subjects with history of prior radiation pneumonitis are not excluded.	□ oui □ non
Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or that may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the subject inappropriate for entry into this study, or could compromise protocol objectives in the opinion of the Investigator and/or Turning Point Therapeutics.	□ oui □ non
Current use or anticipated need for drugs that are known to be strong CYP3A inhibitors or inducers as listed in Appendix 5.	□ oui □ non
Hypersensitivity to the active substance or to any of the excipients.	□ oui □ non
Additional exclusion criteria for subjects participating in the midazolam DDI sub-study: in addition to the strong CYP3A inhibitors or inducers listed in Appendix 5, subjects should not be taking any moderate inhibitors or inducers of CYP3A (moderate CYP3A inhibitors e.g.: erythromycin, verapamil, atazanavir, fluconazole, darunavir, diltiazem, delavirdine, aprepitant, imatinib, tofisopam, ciprofloxacin, cimetidine; moderate CYP3A inducers e.g.: bosentan, efavirenz, etravirine, modafinil) within 2 weeks of the lead-in midazolam dosing and until the DDI assessment portions is completed on Cycle 1 Day 23. Please refer to midazolam product package insert for complete information.	□ oui □ non

Date : _____ Signature de l'investigateur : _____