A Phase 1b, Open-Label Study of the Safety, Pharmacokinetics, and Pharmacodynamics of JNJ-64264681 in Combination with JNJ-67856633 in Participants with Non-Hodgkin Lymphoma and Chronic Lymphocytic Leukemia

Published: 22-03-2021
Last updated: 04-04-2024

The purposes of this trial are:• To find out the side effects (unexpected or unwanted reactions from taking a drug) when JNJ-64264681 and JNJ-67856633 are given in combination. • To find out how and at what dose(s) the combination of JNJ-64264681…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON52350

Source
ToetsingOnline

Brief title
Phase 1b study with JNJ64264681 and JNJ67856633 in patients with NHL en CLL

Condition

- Other condition
- Lymphomas non-Hodgkin's B-cell

Synonym

B-cell non-Hodgkin lymphoma & chronic lymphocytic leukemia

Health condition

Chronic Lymphocytic Leukemia

Research involving
Human

Sponsors and support

Primary sponsor: Janssen-Cilag
Source(s) of monetary or material Support: Farmaceutisch bedrijf: Janssen-Cilag BV

Intervention

Keyword: Chronic Lymphocytic Leukemia, Non-Hodgkin Lymphoma

Outcome measures

Primary outcome

Part A (Dose Escalation) Determine the recommended Phase 2 doses (RP2Ds) of

JNJ-64264681 and JNJ-67856633 when administered together in participants with B

cell NHL and CLL

Part B (Cohort Expansion) Determine the safety of the RP2D(s) for this

combination in different histologies/ participant populations

Secondary outcome

Assess the PK of JNJ-64264681 and JNJ-67856633 when administered together

Assess the PD of JNJ-64264681 and JNJ-67856633 when administered together

Assess the preliminary clinical activity of JNJ-64264681 and JNJ-67856633 when

administered together

Study description

Background summary

A Phase 1b, Open-Label Study of the Safety, Pharmacokinetics, and Pharmacodynamics of JNJ-64264681 in Combination with JNJ-67856633 in Participants with Non-Hodgkin Lymphoma and Chronic Lymphocytic Leukemia
Bruton*s tyrosine kinase (BTK) is a cytoplasmic tyrosine kinase that plays a critical role in B cell activation via the B cell receptor (BCR) signaling pathway. BTK is important for normal B-cell activation and the pathophysiology of B cell malignancies. A few BTK inhibitors have demonstrated clinical activity in non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia (CLL). JNJ-64264681 is a second-generation, orally active, irreversible covalent BTK inhibitor. Given its BTK inhibitory potency, along with nonclinical data to date, JNJ-64264681 is likely to have similar anti-lymphoma activity to already approved BTK inhibitors. Mucosa-associated lymphoid tissue lymphoma translocation protein 1 (MALT1) is a key mediator of the BCR signal transduction pathway positioned downstream of BTK. MALT1 plays a key role in activating the classical nuclear factor kappa-light-chain-enhancer of activated B cells (NF-*B) signaling pathway. As such MALT1 has been shown to play a critical role in supporting tumor growth in different types of lymphoma, including activated B-cell-like subtype of diffuse large B cell lymphoma (DLBCL). JNJ-67856633 is an orally bioavailable, potent, and allosteric inhibitor of MALT1 that has demonstrated promising clinical signals and favorable toxicity profile in a Phase 1 study sponsored by Janssen Pharmaceutical Companies (sponsor). Furthermore, the sponsor has investigated the rationale and synergistic activity of JNJ-64264681 and JNJ-67856633 in preclinical cellular as well as mouse models. This study will evaluate JNJ-64264681 in combination with JNJ-67856633 in a first-in-human study of NHL and CLL

Study objective

The purposes of this trial are:
• To find out the side effects (unexpected or unwanted reactions from taking a drug) when JNJ-64264681 and JNJ-67856633 are given in combination.
• To find out how and at what dose(s) the combination of JNJ-64264681 and JNJ-67856633 should be given for treating patients with B-cell Non-Hodgkin*s Lymphoma (B-cell NHL) and Chronic Lymphocytic Leukemia (CLL).
• To find out how long JNJ-64264681 and JNJ-67856633 stay in and act on the body, and how the body responds to them, when given in combination. This is shown by laboratory blood tests.

Study design

The primary purpose of this study is to determine: the recommended Phase 2 doses (RP2Ds) of JNJ-64264681 and JNJ 67856633 when administered together in participants with B cell non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia (CLL) (Part A - Dose Escalation); and the safety of the RP2Ds for this combination in different histologies/participant populations (Part B - Cohort

Expansion).

Intervention

Participants receive the combination JNJ-64264681 (capsule) and JNJ-67856633 (capsule or tablet) daily or twice daily. The dosage will be determined based on the available data.

Study burden and risks

The viability of 4 different ABC-DLBCL lines and 4 different MCL lines was evaluated in vitro following treatment with different doses of JNJ-64264681 and JNJ-67856633 administered together. Strong synergistic effects of the JNJ-64264681 and JNJ-67856633 combination were observed in 3 DLBCL cell lines carrying CD79b mutations and 1 of 4 MCL cell lines. Treatment with JNJ-64264681 and JNJ-67856633 administered together demonstrated statistically significant TGI compared with vehicle control in 2 CD79b mutant mouse lymphoma models, 1 based on a DLBCL cell line (OCI-LY10) and 1 on a patient-derived DLBCL model LY2298. In both models, the combination of the 2 study drugs showed increased growth inhibition compared
with single agents, and tumor regression in the combination arm. Furthermore, JNJ-64264681 and JNJ-67856633 administered together showed a significant downregulation of IL-10 secretion in the serum of LY2298 tumor-bearing mice to a greater extent than when the drugs were administered alone, demonstrating a biological effect of the combination. There was no significant effect on general health and body weight in any of the arms in both these studies including the combination arms. Taken together, these studies provide support for clinical investigation of the combination therapy
of the BTK inhibitor, JNJ-64264681, and the MALT1 inhibitor, JNJ-67856633, as a valid strategy. in combatting ABC-DLBCL and other B cell malignancies with the potential to delay resistance generation due to stronger anti-tumor effects.
The potential risks for JNJ-64264681 and JNJ-67856633 administered as monotherapy are outlined in section 2.3. JNJ-64264681 and JNJ-67856633 when administered together has not been studied in humans.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. >=18 years of age
2. Eastern Cooperative Oncology Group (ECOG) performance status grade of 0 or 1
3. Cardiac parameters within the following range: corrected QT interval (QTcF) <= 480 milliseconds
4. Participants with B cell non-Hodgkin lymphoma (NHL) must have tumor tissue available at baseline as described in the protocol. This is not required for participants with chronic lymphocytic leukemia (CLL)
5. Women of childbearing potential must agree to use a barrier method of contraception; use a highly effective preferably user-independent method of contraception; not to donate eggs (ova, oocytes) or freeze them for future use for the purposes of assisted reproduction during the study; not to plan to become pregnant; and not to breastfeed

Exclusion criteria

1. Part A and select cohorts in Part B: Prior treatment with JNJ-64264681 or JNJ-67856633. Previously discontinued treatment with a BTK or MALT inhibitor other than JNJ-64264681 or JNJ-67856633 due to participant or doctor choice without evidence of progression or intolerable class-related toxicity will be eligible.
2. Known (active) CNS involvement for dose escalation and specific expansion

cohorts as determined by the SET.
3. Received prior solid organ transplantation.
4. Participant has known allergies, hypersensitivity, or intolerance to JNJ-64264681 or JNJ-6785566 or excipients (refer to the respective IBs).
5. Toxicities from previous anti-cancer therapies that have not resolved to baseline levels, or to Grade <2 (except for alopecia [>=Grade 2], vitiligo [Grade 2] and peripheral neuropathy [Grade 1]).

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-03-2022
Enrollment:	2
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Nap
Generic name:	Nap

Ethics review

Approved WMO

Date:	22-03-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	28-05-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-09-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-09-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-10-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-10-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-02-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-03-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-06-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-07-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	18-08-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-08-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
Other	04657224
EudraCT	EUCTR2020-003149-12-NL
CCMO	NL76498.018.21