Prevention and Treatment of Chemotherapy-Induced Peripheral Neuropathy: Developing Drug and Biological Products in Oncology

Guidance for Industry

DRAFT GUIDANCE

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Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

January 2025
Clinical/Medical

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Prevention and Treatment of Chemotherapy-Induced Peripheral Neuropathy: Developing Drug and Biological Products in Oncology Guidance for Industry[1]

I. INTRODUCTION

This guidance provides recommendations to sponsors for the clinical development of drug and biological products[2] intended for the prevention and treatment of chemotherapy-induced peripheral neuropathy (CIPN) in oncology patient populations. The guidance pertains to development programs for drugs regulated by the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

CIPN can be a painful, disabling, and potentially irreversible condition commonly affecting patients receiving neurotoxic chemotherapies. CIPN is characterized by pain, numbness, tingling, and sensitivity to cold in the hands and feet, and may sometimes extend to the arms and legs. CIPN can persist even after chemotherapy is discontinued. Although CIPN is most frequently a sensory neuropathy, it may be accompanied by motor and autonomic effects of varying intensity and duration. CIPN can negatively affect short- and long-term quality of life and could diminish

[1] This guidance has been prepared by the Oncology Center of Excellence (OCE), Center for Drug Evaluation and Research (CDER), and Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] For the purposes of this guidance, references to *drug* or *drugs* include drug products approved under section 505 of the Federal Food, Drug, and Cosmetic (FD&C) Act (21 U.S.C. 355) and biological products licensed under section 351 of the Public Health Service Act (42 U.S.C. 262).

survival by potentially increasing chemotherapy treatment interruptions, dose reductions, and discontinuations.

CIPN varies in pathogenesis, clinical presentation, severity, and natural history. Beyond exposure to chemotherapy, there are likely other factors involved in the pathogenesis of CIPN, such as pharmacogenomic effects and genetic risk factors. The pathogenesis of CIPN is complex, involving changes in ion channels, transient receptor potential channels, mitochondrial dysfunction, and immune cell interactions.[3] Investigational drugs for CIPN prevention and treatment may target multiple mechanisms or pathways. There is a concern that CIPN-mitigating drugs may decrease the efficacy of cancer treatment or potentially promote tumor growth.

Considerations and recommendations for CIPN drug development and clinical trials are outlined herein. This guidance focuses on (1) drugs intended to prevent or lessen the severity of CIPN during cancer treatment and (2) recommendations pertinent to drugs intended to lessen the severity of CIPN after cancer treatment is complete. Conducting well-designed trials is crucial to increasing the availability of CIPN drugs for patients.

III. RECOMMENDATIONS AND CONSIDERATIONS

A. Trial Population and Design

- Drug development programs for CIPN should account for potential concerns of diminished efficacy of cancer treatment or the promotion of tumor growth.

- Before initiating clinical trials, the sponsor should conduct proof-of-concept nonclinical[4] studies to (1) investigate the mode of action of the drug, (2) demonstrate that the drug does not promote tumor growth, and (3) demonstrate that the drug does not interfere with cancer treatments. The clinical trial design can further address any potential interference with cancer treatments or the promotion of tumor growth.

    - If no clinical data exist on the effect of the investigational drug in patients with cancer, initial clinical investigations of the CIPN investigational drug should include only participants with unresectable or metastatic (incurable) cancer. Patients with early-stage (curable) cancer should not be included in the initial clinical investigation as any impact on the efficacy of cancer treatment could compromise a patient's chance for cure.

[3] Colvin LA, 2019, Chemotherapy-Induced Peripheral Neuropathy: Where Are We Now? Pain, 160(Suppl 1): S1-S10.

[4] We support the principles of the "3Rs," to reduce, refine, and replace animal use in testing when feasible. We encourage sponsors to consult with us if it they wish to use a non-animal testing method they believe is suitable and adequate. We will consider if such an alternative method could be assessed for equivalency to an animal test method.

  - If nonclinical data and initial clinical data in participants with unresectable or metastatic (incurable) cancer for the CIPN investigational drug do not show a potential interaction with cancer treatment or promotion of tumor growth, subsequent trials of the CIPN drug may occur in participants with early-stage (curable) disease, with appropriate justification.

  - As with all FDA-regulated clinical trials, investigators must obtain informed consent from each participant (or their legally authorized representative) in accordance with 21 CFR part 50 prior to their enrollment in a CIPN trial. Among other information, participants must be informed of "any reasonably foreseeable risks" as part of the informed consent process.[5] Regardless of the cancer stage of the potential CIPN trial participant, this would generally include the possible risk that the investigational drug may worsen their cancer either through interference with cancer treatment or promotion of tumor growth.

- CIPN trials should be randomized to compare participants receiving the CIPN investigational drug to a control group to assess whether the treatment effect is attributable to the CIPN drug rather than the natural history of CIPN. CIPN may improve without intervention after chemotherapy is withdrawn, although improvement is less likely for patients with persistent CIPN long after completing chemotherapy.

- In CIPN trials, the participant population should be sufficiently homogenous with respect to tumor type and cancer treatment for several reasons:

  - CIPN resulting from various cancer treatments and different tumor types may be inherently different due to underlying pathology and side effect profiles of the cancer treatments. Therefore, the response to the CIPN drug may not be the same.

  - There is the potential for drug interactions between cancer treatments and investigational drugs for CIPN, which can vary based on the drugs under evaluation.

- If a CIPN trial enrolls participants with multiple tumor types or who receive different cancer treatments, tumor type or cancer treatment may be included as a stratification factor.

B. Primary and Secondary Endpoints

- FDA has no defined set of recommended clinical outcome measures to assess efficacy for trials intended to support approval of drugs for the prevention or treatment of CIPN. Patient-reported outcomes, clinician-reported outcomes, or objective measures of patient function that measure symptoms or functions relevant to CIPN may be considered as efficacy endpoints. The selection of appropriate efficacy endpoints should consider the manifestations of CIPN that the investigational drug is anticipated to impact (e.g.,

[5] 21 CFR 50.25

sensory, motor or autonomic deficits) and whether the investigational drug is intended to show benefit on existing symptoms of CIPN or prevent the development of CIPN. Sponsors should consult FDA early in the process of the selection and/or development of efficacy endpoints for CIPN.

- A standardized assessment of dosage modifications due to peripheral neuropathy could be a secondary endpoint. Ideally, effective CIPN drugs would minimize chemotherapy dosage interruptions, dose reductions, and drug discontinuations.

- For a trial intended to support a marketing application, oncology-specific endpoints to assess the efficacy of cancer treatments should be included as secondary endpoints to evaluate the potential interference with cancer treatment or the promotion of tumor growth by the CIPN drug.

  - In the metastatic cancer setting, these endpoints may include overall response rate, duration of response, progression-free survival, and overall survival (OS).

  - In the early-stage setting, these endpoints may include disease-free survival, event-free survival, and OS.

- For a trial intended to support a marketing application, the oncology-specific endpoint(s) should be included as part of the statistical hierarchy and evaluated with appropriate alpha allocation. While it may not be feasible to adequately power for oncology-specific endpoint(s) in CIPN trials, it will be important to evaluate whether the oncology-specific endpoint(s) at the time of the primary analysis shows a detrimental effect of the CIPN drug.

  - A plan for long-term follow-up should be pre-specified and allow for sufficient maturity to evaluate whether the oncology-specific endpoint(s) shows a detrimental effect of the CIPN drug. A formal interim analysis of oncology-specific endpoint(s) should be conducted at the time of the CIPN primary efficacy analysis. The plan for long-term follow-up should be discussed with the Agency prior to initiation.