

SUMMARY

Amgen appreciates the opportunity to comment on ICER's *Draft Background and Scoping Document for Chemotherapy-Induced Neutropenia*. Patients experiencing neutropenia have an absolute neutrophil count lower than 1500/microliter¹, and this continues to be a serious side-effect of many myelosuppressive chemotherapy regimens.^{2,3} It is not uncommon for patients to develop febrile neutropenia (FN) to such a degree that it leaves patients susceptible to serious complications of infection that could lead to hospitalization or even death.^{4,5} Susceptibility to infections sharply increases when neutrophil counts fall, and approximately 7-22% of cancer patients who undergo chemotherapy require hospitalization for FN.^{6,7} Because of this, hundreds of thousands of patients are hospitalized for chemotherapy-induced neutropenia each year. This causes an untold burden on patients as well as the health system, with the average length of stay for a patient hospitalized for FN ranging from 7-7.5 days.^{8,9} Neulasta® (pegfilgrastim) is a leukocyte growth factor treatment indicated to 1) decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia, and 2) increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome).¹⁰ Multiple clinical studies have demonstrated Neulasta's ability to prevent the potentially deadly consequences of myelosuppressive chemotherapy by reducing the incidence of FN.^{11,12}

Amgen is committed to continuing its rich history of discovery, research and development of treatments for neutropenia. As the manufacturer of Neulasta®, Amgen has been the industry leader with over thirty years of experience in this space and we would like to highlight important recommendations for ICER's consideration:

- 1. The comparator for plinabulin should be pegfilgrastim pre-filled syringe and based on the PROTECTIVE-2 trial, in accordance with the NCCN® Guidelines for prophylactic granulocyte colony-stimulating factor (G-CSF) use.¹³**
- 2. The analysis should apply only clinically-validated regimens wherein prophylactic G-CSF (*i.e.*, pegfilgrastim, filgrastim, and their biosimilars) is administered the day after chemotherapy, consistent with the pivotal PROTECTIVE-2 clinical trial, labeled indication, and U.S. practice guidelines, including NCCN®.¹⁴**
 - a) Same-day administration of pegfilgrastim is linked to increased incidences of FN, exposing patients to further potential harms compared to next-day administration.**

Below we outline these recommendations in more detail.

RECOMMENDATIONS

- 1. The comparator for plinabulin should be pegfilgrastim pre-filled syringe and based on the PROTECTIVE-2 trial^{15,16} in accordance with the NCCN[®] Guidelines¹⁷ for prophylactic G-CSF use.**

The preferred option for patients at high risk for developing FN (>20% risk of FN) is prophylactic G-CSF (e.g., pegfilgrastim and filgrastim as well as their biosimilars).^{1,18,19,20} This is a result of several large, randomized trials that have demonstrated a significant reduction in FN incidence following next-day G-CSF administration.²¹ The PROTECTIVE-2 pivotal trial adheres to this with a comparator arm consisting of a combination treatment of plinabulin plus pegfilgrastim vs. a control arm of pegfilgrastim, where pegfilgrastim in either arm is administered on day one after a chemotherapy cycle of docetaxel, doxorubicin, and cyclophosphamide (TAC).^{22,23} This is also in accordance with the NCCN[®] Guidelines²⁴, which include pegfilgrastim as well as biosimilars as an appropriate treatment for FN.²⁵ As randomized clinical trials are the gold standard for establishing efficacy and safety, we recommend ICER conduct their base case economic analysis with an intervention arm of plinabulin + pegfilgrastim vs. pegfilgrastim alone.

- 2. The analysis should apply only clinically-validated regimens wherein prophylactic G-CSF (i.e., pegfilgrastim, filgrastim, and their biosimilars) is administered the day after chemotherapy consistent with the pivotal PROTECTIVE-2 clinical trial, labeled indication, and U.S. practice guidelines, including NCCN[®].²⁶**
 - a) Same-day administration of pegfilgrastim is linked to increased incidences of FN compared to next-day administration, thereby exposing patients to unnecessary further potential harms.**

U.S., international Guidelines, large randomized clinical trials, and several RWE studies have established the safety and efficacy of next-day pegylated G-CSF. Neutropenia and febrile neutropenia (FN) are common side effects of cancer chemotherapy treatments, often leading to life-threatening adverse events requiring hospitalization.²⁷ Pegylated G-CSF is indicated to boost neutrophil count to prevent infection.²⁸

Same-day administration of pegfilgrastim is associated with greater FN-related hospitalization.²⁹ While there have been discussions in the supportive oncology care field for a same-day pre-filled pegfilgrastim administration to avoid an extra trip to an infusion center,³⁰ suboptimal administration of pegfilgrastim (any day other than the next day after chemotherapy) can lead to an increased risk of FN.³¹ Randomized clinical studies and real-world evidence (RWE) report higher rates of FN for same-day pegfilgrastim administration following chemotherapy as opposed to next-day pegfilgrastim administration, as shown in Table 1. These data provide the evidence base for recently updated American Society of Clinical Oncology (ASCO)³² and European Society for Medical Oncology (ESMO)³³ clinical practice guidelines, which recommend pegylated G-CSF administration 24 hours after administering myelotoxic chemotherapy.

¹ As per NCCN[®] guidelines, filgrastim and its biosimilars are also appropriate treatments options.

Furthermore, as stated above, the PROTECTIVE-2 pivotal trial used a combination of same-day plinabulin plus pegfilgrastim on day one after a chemotherapy cycle and not on the same day of chemotherapy. Therefore, we recommend ICER include next-day use of prophylactic G-CSF, reinforcing research that shows this is best for patients.

CONCLUSION

We appreciate ICER’s assessment of new treatments for FN and look forward to working with ICER in this assessment. In summary, to ensure greater accuracy and validity, ICER should include comparators in alignment with the PROTECTOR-2 pivotal trial and current NCCN® guidelines and limit the assessment to next-day use of G-CSF consistent with clinical data, product labeling, and U.S. and international guidelines.

APPENDIX

In Table 1, we have provided trial data and retrospective cohort studies of single arm same-day administration of pegfilgrastim along with same-day vs. next-day comparison studies to allow for a side-by-side comparison of all the studies.

Of particular note in the same-day studies:

- *Leiva et al.* – FN Incidence rate for all cycles was the same as placebo
- *Vraney et al.* - 72% of patients considered at *mild* FN Risk

Table 1: Literature Evaluating Administration of Pegfilgrastim – Same-Day vs. Next-Day

Authors (Year)	Population	Regimen	Outcomes
Pegfilgrastim same-day vs. next-day administration studies			
Systematic Review			
Lyman et al. (2017) ³⁴ Link	Study: A systematic review of 11 studies (4 randomized/single-arm prospective studies, 7 retrospective studies). Population: Cancer types: non-small cell lung cancer (NSCLC), breast cancer, non-Hodgkin lymphoma (NHL), ovarian cancer, head and neck cancer, urothelial carcinoma, gynecologic malignancies, and other solid tumor types. Chemotherapy: Not specified.	11 studies <ul style="list-style-type: none"> • 9 studies (same-day vs. next-day pegfilgrastim) • 1 study (same-day vs. next-day pegfilgrastim or filgrastim. • 1 study (day 3 vs. day 7 filgrastim or pegfilgrastim with docetaxel, cisplatin, plus 5-fluorouracil (DCF) on days 1 to 5). 	<ul style="list-style-type: none"> • Same-day administration associated with higher rates and longer duration of neutropenia/febrile neutropenia (FN) in 6/11 studies • Some studies showing lower/comparable rates with same-day had limitations (low sample size or evaluating day 3 vs. day 7 administration with DCF)
Ma et al. (2021) ³⁵ Link	Study: Systematic review and meta-analysis of currently available evidence (1 randomized controlled trial	13 studies (2004-2019), sample sizes ranged from 24 to 53,814 <ul style="list-style-type: none"> • 1 RCT • 11 cohort studies 	<ul style="list-style-type: none"> • The patients administered same-day pegfilgrastim had a significantly higher FN rate than those receiving next-day pegfilgrastim (OR =1.64,

	(RCT) and 12 observational studies) Population: Cancer types: Breast cancer, NHL, non-small cell lung cancer (NSCLC), ovarian cancer, gynecological malignancies, lymphoma, ovarian cancer, colorectal cancer.	<ul style="list-style-type: none"> • 1 control study <p>All 13 studies: a dosage of 6 mg of pegfilgrastim was administered.</p> <ul style="list-style-type: none"> • Same-day pegfilgrastim was offered on the last day of chemotherapy. • Next-day group, pegfilgrastim was injected at least 24-72 hours later or on days 2-4 after chemotherapy completion. 	95% CI 1.38-1.98, p<0.00001). <ul style="list-style-type: none"> • Subgroup (breast cancer): substantially higher FN rate was observed in the same-day pegfilgrastim group than in the next-day pegfilgrastim (OR = 5.5, 95% CI 2.29-13.23, p=0.0001). • Subgroup (lymphoma): higher FN rate was seen in the same-day pegfilgrastim group than in the next-day pegfilgrastim group (OR=1.53, 95% CI 1.00-2.34, p=0.05).
Retrospective Cohort Studies			
Weycker et al. (2018) ³⁶ Link	Study: Retrospective cohort, claims analysis (Medicare claims between Jan 2007- Sept 2015.) Location: US N= 65,003 patients (261,184 cycles) <ul style="list-style-type: none"> • Same-day: 3,340 • Day 1-3: 61,663 Population: Cancer types: non-metastatic breast cancer, NHL Chemotherapy: Those of intermediate/high risk for FN, common regimens – docetaxel / cyclophosphamide (TC), docetaxel/ carboplatin/ trastuzumab (TCH) TAC, dose dense doxorubicin/ cyclophosphamide/ paclitaxel (AC-T)/ AC and rituximab/ cyclophosphamide/ doxorubicin/ vincristine/ prednisone (CHOP-R)	Same-day pegfilgrastim (day 0) vs. days after (day 1-3).	FN Incidence for Cycle 1 <ul style="list-style-type: none"> • Same-Day: 11.4% • Day 1-3: 8.4% FN Incidence for All Cycles <ul style="list-style-type: none"> • Same-Day: 7.7% • Day 1-3: 6%
Weycker et al. (2017) ³⁷ Link	Study: Retrospective cohort, claims analysis (2 claim repositories for private US health plans between Jan 2010- March 2016.) Location: US N= 53,814 patients (217,273 cycles) <ul style="list-style-type: none"> • Same-Day: 4726 • Day 1-3: 48,740 • Day 4-5: 348 	Same-day pegfilgrastim (day 0), day 1-3 following chemotherapy or days 4-5 following chemotherapy.	FN Incidence for Cycle 1 <ul style="list-style-type: none"> • Day 0: 3.4% • Day 1-3: 2.5% • Day 4-5: 6.0% FN Incidence for All Cycles <ul style="list-style-type: none"> • Day 0: 2.2% • Day 1-3: 1.8% • Day 4-5: 33.4%

	<p>Population: Cancer types: non-metastatic breast cancer (83%), NHL (12%), non-metastatic lung cancer (2%), non-metastatic ovarian cancer (3%).</p> <p>Chemotherapy: Those of intermediate/high risk for FN.</p>		
Same-Day Pegfilgrastim Trial Data			
<p>Vogel et al. (2005)³⁸ Link</p>	<p>Study: Prospective Phase 3 (Breast Cancer)</p> <p>Location: US and EU</p> <p>N= 928 patients (>838 Cycles)</p> <ul style="list-style-type: none"> • Placebo: 465 • Next-Day Pegfilgrastim: 463 	<p>Next-day pegfilgrastim vs Placebo in patients receiving docetaxel chemotherapy</p>	<p>FN Incidence for Cycle 1</p> <ul style="list-style-type: none"> • Pegfilgrastim: <1% • Placebo: 11% <p>FN Incidence for All Cycles</p> <ul style="list-style-type: none"> • Pegfilgrastim: 1% • Placebo: 17%
<p>Leiva et al. (2021)³⁹ Link</p>	<p>Study: Retrospective, single-institution EHR Chart review</p> <p>N= 55 breast cancer patients</p>	<p>Same-day pegfilgrastim-cbqv (biosimilar)</p>	<p>FN Incidence For All Cycles</p> <p>Same-Day biosimilar pegfilgrastim: 16.4% (same rate as placebo arm of pivotal trial)</p>
<p>Vraney, et al. (2021)⁴⁰ Link</p>	<p>Study: Retrospective, single-institution chart review</p> <p>N= 114 patients, 384 cycles Lung Cancer (72% of patients considered at <i>mild</i> FN Risk)</p>	<p>Same-day pegfilgrastim in lung cancer patients at mild risk for FN</p>	<p>FN Incidences</p> <ul style="list-style-type: none"> • Cycle 1: 1% • All Cycles: 2% <p>Grade 3/4 CIN</p> <ul style="list-style-type: none"> • Cycle 1: 10% • All Cycles: 10%
<p>Bartels et al. (2021)⁴¹ Link</p>	<p>Study: Retrospective cohort study (Analysis between October 1, 2013- October 2020)</p> <p>Location: US</p> <p>N= (100 cycles of reduced dose of cyclophosphamide, doxorubicin, vincristine, and prednisone (miniR-CHOP)).</p> <p>Population: Cancer type: diffuse large B-cell lymphoma (DLBCL).</p> <p>Chemotherapy: Incidence of FN across all cycles of chemotherapy.</p>	<p>100 cycles of miniR-CHOP, pegfilgrastim was administered on same-day of chemotherapy in 95 cycles and 5 cycles on the next-day of chemotherapy.</p>	<p>OVERALL:</p> <p>Incidence of FN:</p> <ul style="list-style-type: none"> • Same-Day: 5.3% • Next-Day: 0.0 <p>1st cycle of chemotherapy:</p> <p>FN incidence:</p> <ul style="list-style-type: none"> • Same-Day: 14.3% • Next-Day: 0.0 <p>CIN 3/4:</p> <ul style="list-style-type: none"> • Same-Day: 21.4% • Next-Day: 0.0

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September 14, 2021

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Re: BeyondSpring Pharmaceutical, Inc.’s Comments on ICER’s Draft Background and Scope to Assess Novel Agents to Prevent Chemotherapy-Induced Neutropenia

Dear Dr. Pearson,

BeyondSpring Pharmaceuticals, Inc. (“BeyondSpring”) is pleased to provide comments on the Institute for Clinical and Economic Review’s (ICER’s) assessment of *Novel Agents to Prevent Chemotherapy-Induced Neutropenia: Draft Background and Scope* released on August 25th, 2021.¹ As acknowledged by ICER in its draft scope, chemotherapy-induced neutropenia (CIN) remains a significant health, quality of life, and financial burden for patients undergoing cytotoxic chemotherapy. We believe that a particularly high unmet need remains for patients during the “Neutropenia Vulnerability Gap,” the seven-day period following myelosuppressive chemotherapy administration, when patients are most likely to experience CIN.

We have provided our comments below on the scope outlined for ICER’s review of novel agents to prevent CIN. We wish to highlight differences in sponsor-recommended labelling language between plinabulin and trilaciclib and believe that it would be misleading to directly or indirectly compare outcomes across both treatments. We also encourage ICER to consider benefits from novel agents in real-world treatment settings that may not be adequately captured in controlled clinical trial settings. For example, we would like to highlight the potential incremental societal value from greater health equity and fairness from plinabulin which may be difficult to fully capture in structured cost-effectiveness analysis.

Population

Plinabulin has been granted Breakthrough Therapy designation and Priority Review by the U.S. FDA with a PDUFA date of November 30, 2021. Although plinabulin is still under review by the FDA, consideration of plinabulin has been requested for use in combination with G-CSFs for “concurrent administration with myelosuppressive chemotherapeutic regimens in patients with non-myeloid malignancies for the prevention of CIN.”² Within the population of focus for ICER’s review (“adults ≥ 18 years of age with ECOG performance status of 0 or 1 at intermediate or high risk for CIN”)¹, we believe that plinabulin will offer substantial incremental benefits to the subset of patients who do not receive one or more planned G-CSF administrations as intended due to access barriers or whose G-CSF is not adequately self-administered outside of physician offices.^{3,4} Because risk of missing G-CSF administrations is expected to disproportionately impact patients with sub-optimal access to healthcare services, we believe that plinabulin will play a role in reducing inequities in cancer care and we encourage ICER to consider these population factors in its assessment.^{5,6}

Recommendation: We encourage ICER to consider the potential role of plinabulin in reducing health inequities among patients with sub-optimal access to healthcare services.

Interventions

In its draft scope, ICER suggests that the following plinabulin interventions will be considered in its clinical evidence review and compared “to each other and to standard dose (6 mg IV) pegfilgrastim (brand name or biosimilars) alone”:¹

- Plinabulin 40mg IV
- Plinabulin 40 mg IV plus pegfilgrastim 6 mg IV

We would like to highlight that the clinical benefit of plinabulin has been demonstrated in several clinical trials of different designs, which consistently provide evidence of plinabulin’s effectiveness as a monotherapy or combination therapy with pegfilgrastim.

For example, the PROTECTIVE-1 clinical trial was a non-inferiority study designed to evaluate plinabulin monotherapy compared to pegfilgrastim among solid tumor cancer patients treated with docetaxel.⁷ Separately, the PROTECTIVE-2 clinical trial was a superiority study designed to evaluate plinabulin in combination with pegfilgrastim compared to pegfilgrastim alone among breast cancer patients treated with docetaxel, doxorubicin, and cyclophosphamide.⁸ Finally, the DUBLIN-3 clinical trial was a superiority study designed to evaluate overall survival among non-small cell lung cancer (NSCLC) patients treated with docetaxel.⁹ We note that patients in the DUBLIN-3 clinical trial received a higher dose of plinabulin (30 mg/m² twice per cycle) compared to the PROTECTIVE-1 and PROTECTIVE-2 clinical trials (40mg).

Recommendation: Data from all plinabulin clinical trials should be considered in the overall scope of ICER’s evaluation.

Comparators

In its draft scope, ICER proposes to compare the following “interventions to each other and to standard dose (6 mg IV) pegfilgrastim (brand name or biosimilars) alone” in its clinical review:¹

- Plinabulin 40mg IV
- Plinabulin 40 mg IV plus pegfilgrastim 6 mg IV
- Trilacicib (Cosela™)

Trilaciclib is a kinase inhibitor indicated to “decrease the incidence of chemotherapy-induced myelosuppression in adult patients when administered prior to a platinum/etoposide-containing regimen or topotecan-containing regimen for extensive-stage small cell lung cancer”.¹⁰ In contrast, plinabulin is an investigational selective immunomodulating microtubule-binding agent (SIMBA) with a requested labeled indication for use in combination with G-CSFs for “concurrent administration with myelosuppressive chemotherapeutic regimens in patients with non-myeloid malignancies for the prevention of CIN.”² We believe it misleading to conduct direct or indirect comparisons of clinical evidence and/or comparative value across both agents.

Recommendation: Direct or indirect comparisons of clinical evidence and value between plinabulin and trilaciclib may be misleading.

Outcomes

ICER includes ‘delayed or reduced dose chemotherapy’ in its list of patient-important outcomes to be included in its review.¹ In addition to chemotherapy delays and dose reductions, we encourage ICER to account for chemotherapy discontinuation which can impact cumulative chemotherapy dose intensity and have detrimental impacts on long-term patient survival and progression outcomes.^{11,12,13} We would also like to highlight the need for incorporating real-world data on chemotherapy dose disruption into ICER’s assessment, as real-world treatment patterns may be substantially different compared to treatment patterns observed in controlled clinical trial settings.

As discussed in ICER’s draft scoping document, novel agents for preventing CIN are also expected to provide incremental anticancer benefits which may improve patient survival and disease progression outcomes. For example, the DUBLIN-3 clinical trial assessed the potential for incremental anticancer benefits from plinabulin.⁹ To conduct a comprehensive review of the potential benefits from plinabulin, we encourage ICER to incorporate available evidence related to anticancer benefits in its assessment. We will be releasing results from a proffered paper presentation on the DUBLIN-3 trial at the European Society for Medical Oncology (ESMO) on September 20, 2021, which will provide additional data on plinabulin anticancer benefits.

We also appreciate that ICER plans to assess patient-important outcomes outside of direct medical costs, such as quality of life impacts from reduced bone pain and indirect productivity impacts. We encourage ICER to additionally consider potential impacts from alleviating the burden of caregivers for solid tumor cancer patients,^{14,15} as well as the incremental societal value of added “insurance” from preventing CIN and febrile neutropenia among a patient population with particularly severe disease, high unmet need, and limited existing treatment options.¹⁶

Finally, we encourage ICER to consider potential system-wide cost-efficiencies which may be gained in real-world settings from enhancing chemotherapy treatment with plinabulin. Enabling providers to more safely and consistently administer chemotherapy may result in greater preference for chemotherapy over costlier alternatives earlier in patients’ course of care.

Recommendation: Add chemotherapy discontinuation and anticancer benefits to outcomes assessed, as well as indirect benefits related to alleviating caregiver burden and improving societal value. Incorporate real-world data regarding treatment patterns in non-trial settings.

We hope that the above recommendations will be helpful to ICER in developing its review of novel agents to prevent CIN. We look forward to reviewing ICER’s final scope and providing additional feedback throughout the course of ICER’s assessment. Please do not hesitate to contact me at ylelorier@beyondspringpharma.com or 645-221-0752 with any questions.

Sincerely,



Yvette LeLorier

Director, Clinical Research – HEOR/PRO

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September 14, 2021

Steven D. Pearson, MD, MSc
President, Institute for Clinical and Economic Review
Two Liberty Square, 9th Floor, Boston, MA 02109

Re: ICER's Assessment of Treatments for Chemotherapy-Induced Neutropenia

Dear Dr. Pearson,

G1 Therapeutics appreciates the opportunity to provide comments in response to the Institute for Clinical and Economic Review's (ICER) Draft Scoping Document on the assessment for treatments for chemotherapy-induced neutropenia (CIN).

G1's suggestions for updates to ICER's scoping document are organized below.

1. Trilaciclib should not be included in the plinabulin review. The benefits of trilaciclib are broader than the scope of this assessment – which is only chemotherapy-induced neutropenia

- Trilaciclib is indicated to decrease the incidence of chemotherapy-induced myelosuppression in adult patients when administered prior to a platinum/etoposide-containing regimen or topotecan-containing regimen for extensive-stage small cell lung cancer (ES-SCLC).¹
- Myelosuppression is a condition in which bone marrow activity is decreased, resulting in fewer white blood cells (neutropenia), and also in fewer red blood cells (anemia) and platelets (thrombocytopenia).
- Trilaciclib's mechanism of action helps protect hematopoietic stem and progenitor cells (HSPCs) in the bone marrow, to reduce chemotherapy-induced myelosuppression which can manifest as hematologic abnormalities including neutropenia, anemia, and thrombocytopenia.² The clinical trials for trilaciclib were based on endpoints across multiple blood cell lineages.²⁻⁴
- For key differences between trilaciclib and plinabulin see Appendix Table 1.

2. We suggest that ICER change the title of the assessment to represent trilaciclib

As mentioned above, trilaciclib was studied across multiple endpoints and affects other hematological adverse events (anemia, thrombocytopenia) associated with chemotherapy in ES-SCLC in addition to neutropenia.^{2,3} Therefore, we suggest changing the title to “Novel agents to prevent chemotherapy-induced cytopenia” or “Novel agents to prevent chemotherapy-induced myelosuppression” to better reflect the comprehensiveness of this review.

3. We suggest that ICER assess trilaciclib and plinabulin separately, with different clinical assessment and economic models, and their results should not be listed together to avoid confusing readers of the ICER report

- Plinabulin is being investigated for CIN reduction in non-small cell lung cancer, breast cancer and prostate cancers, with docetaxel or TAC (Docetaxel, doxorubicin, cyclophosphamide) as chemotherapy backbone.⁵⁻⁷

- Considering their unique indications and target populations, trilaciclib and plinabulin should be evaluated separately, with individual clinical and cost effectiveness assessment and different model structures and health states.
- No comparison should be made between trilaciclib and plinabulin in the entire assessment.
- The results for the separate trilaciclib and plinabulin reviews should not be displayed side by side in the same tables or sections. This will avoid readers being confused and seeing the two treatments as having comparable indications or usages.

4. Suggestions for the scope of clinical evidence review for trilaciclib

- Population: adult patients with ES-SCLC receiving a platinum/etoposide-containing regimen as first-line chemotherapy
 - This is consistent with the trilaciclib indication
 - We expect the majority of ES-SCLC patients in clinical practice will receive (or are receiving) a platinum/etoposide-containing regimen as first-line chemotherapy, based on real-world studies of electronic health records data from community oncology practice (approximately 95% received platinum/etoposide-containing regimen at the time of chemotherapy initiation, G1 Therapeutics data on file)
- Intervention: trilaciclib (240 mg/m²) intravenous infusion
- Comparators: trilaciclib + chemotherapy vs. placebo + chemotherapy
 - Placebo + chemotherapy was the comparator arm in all trilaciclib clinical trials²⁻⁴
- Outcomes:
 - Severe neutropenia, defined as Grade 3 or higher based on National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE)⁸, see Appendix Table 2 for definitions
 - Duration of severe neutropenia
 - Febrile neutropenia (based on CTCAE)
 - We suggest differentiating between severe CIN without and with fever (febrile neutropenia, FN). For example, on page 1, paragraph 2: the text described risk levels (<10%, 10-20%, >20%) in terms of CIN risk. However, according to the US guidelines, the risk level is for FN risk – i.e., how myelotoxic is a regimen in terms of its likelihood of causing FN⁹
 - Severe anemia (defined as Grade 3 or higher based on CTCAE)
 - Severe thrombocytopenia (defined as Grade 3 or higher based on CTCAE)
 - Delayed chemotherapy
 - Dose reduction in chemotherapy
 - Hospitalization due to chemotherapy-induced myelosuppression (including neutropenia, anemia, and thrombocytopenia) or sepsis
 - Granulocyte colony-stimulating factor (G-CSF) administration
 - Erythropoiesis-stimulating agent (ESA) administration
 - Red blood cell (RBC) transfusion
 - Quality of life
- Note that occurrence of grade 3 or 4 hematological laboratory abnormalities was a secondary outcome in the registrational trials, as were RBC transfusions, G-CSF administrations, and occurrence of FN. The occurrence and incidence of hospitalization

due to chemotherapy-induced myelosuppression or sepsis, chemotherapy exposure, dose reductions and interruptions were evaluated as part of the safety assessment.³

5. Suggestions for the economic model for trilaciclib

- Target Population: adult patients with ES-SCLC receiving a platinum/etoposide-containing regimen as first-line chemotherapy
- Intervention arm: trilaciclib + chemotherapy
- Comparator arm: placebo + chemotherapy
- Model Structure:
 - In the “Scope of Comparative Value Analyses” section, the committee mentioned “the model structure will be based in part on a literature of prior published models of prevention of CIN” and cited references 14-23. Reference 14-22 were models for neutropenia specific for cancer indications other than ES-SCLC, e.g., breast cancer and non-Hodgkin lymphoma (nHL). Model structures in these prior studies are not applicable for trilaciclib given the difference in its target population and the benefit of multilineage myelosuppression mentioned above. Reference 23 is a retrospective trial-based economic analysis in the SCLC population, not a modeling study.
 - The prior CIN models in breast cancer and/or nHL incorporated different model structures to simulate patients on chemotherapy and off chemotherapy. Conceptually, the on-chemotherapy and off-chemotherapy model design may be leveraged for the review for trilaciclib. However, a few assumptions and health states may not be applicable or may require modification to fit ES-SCLC. Key considerations and initial thinking of the model design are described below:
 - During the on-chemotherapy stage, definitions of health state should match the indication and multiple lineage endpoints of trilaciclib. In addition to the health states mentioned in the draft scope, we suggest replacing FN with severe neutropenia including FN, and also include severe anemia, severe thrombocytopenia, as well as multiple (e.g., two or three) cytopenia conditions as additional health states. Severe condition will be defined as Grade 3 or higher based on CTCAE.
 - FN specific costs and disutility could either be modeled as a separate health state from severe neutropenia, or could be accounted for in the calculation of weighted average costs and quality adjusted life years (QALY) associated with severe neutropenia with and without FN. If FN is not modeled as a standalone health state, the weighted average calculations should consider different FN incidence and the duration of treatment/hospitalization required for FN by trilaciclib versus placebo.
 - In the prior CIN models, death from cancer was not included during the on-chemotherapy stage. Given the rapid disease progression of the target population for trilaciclib, death from cancer during chemotherapy should be considered.
 - During the on-chemotherapy stage, treatment discontinuation should be considered as a health state to account for patients who enter the off-chemotherapy stage at each cycle due to cytopenia events and/or other reasons. In addition, the impact of dose reduction on survival should be taken into consideration.

Appendix

Table 1. Trilaciclib and plinabulin should not be compared, given the difference in tumor type, chemotherapy backbone, and outcomes²⁻⁷

	Plinabulin	Trilaciclib
Different Tumor type	NSCLC, breast cancer, prostate cancer assessed in clinical trials	ES-SCLC (indicated condition)
Different Chemotherapy Backbone	Docetaxel, TAC (Docetaxel, doxorubicin, cyclophosphamide)	Carboplatin/etoposide-containing regimen and topotecan-containing regimen
Interventions in clinical trials	<ul style="list-style-type: none"> • Plinabulin + chemotherapy vs. pegfilgrastim + chemotherapy (Protective-1) • Plinabulin + chemotherapy + pegfilgrastim vs. pegfilgrastim + chemotherapy (Protective-2) 	<ul style="list-style-type: none"> • Trilaciclib + chemotherapy vs. placebo + chemotherapy
Different Outcomes/benefits	<ul style="list-style-type: none"> • Chemotherapy-induced neutropenia 	<ul style="list-style-type: none"> • Chemotherapy-induced myelosuppression • Manifestations of chemotherapy induced myelosuppression include impacts on multiple blood cell lineages: anemia, thrombocytopenia and neutropenia

Abbreviations: NSCLC: non-small cell lung cancer; ES-SCLC: extensive-stage small cell lung cancer

Table 2. NCI CTCAE Definitions of Hematologic Toxicity⁸

Blood Element	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Neutrophils	<LLN to 1500/microL	1000 to 1500/microL	500 to 1000/microL	<500/microL	-
Platelets	LLN to 75,000/microL	50,000 to 75,000/microL	25,000 to 50,000/microL	<25,000/microL	-
Hemoglobin	<LLN to 800/microL	8.0 to 10.0 g/dL	<8.0 g/dL	Life-threatening consequences, urgent intervention indicated	Death
Febrile neutropenia	-	-	ANC <1000/microL with a single temperature >38.3°C (100.4°F) or a sustained temperature ≥38°C (100°F) for more than one hour	Life-threatening consequences, urgent intervention indicated	Death

Abbreviations: NCI CTCAE: National Cancer Institute Common Technology Criteria for Adverse Events; LLN: lower limit of normal; ANC: absolute neutrophil count.

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**Comment on the Draft Scoping Document
Novel Agents to Prevent Chemotherapy-Induced Neutropenia
Institute for Clinical and Economic Review (ICER)**

Setting the scene:

Despite substantial progress in precision medicine and immunotherapy, chemotherapy remains the foundation stone of treatment for most cancers. However, chemotherapy is often associated with severe side effects that can affect the patient's quality of life (QoL), often compromising the patient's willingness to continue with, and successfully complete, treatment.

Cytotoxic chemotherapies are not selective. Proliferating hematopoietic stem and progenitor cells in the bone marrow are particularly susceptible to chemotherapy-induced damage. Therefore, one of the most common side effects of chemotherapy is myelosuppression, which usually expresses as neutropenia, anemia, thrombocytopenia, and/or lymphopenia. The magnitude of damage to neutrophils, red blood cells, platelets, and/or lymphocytes depends on the chemotherapy regimen used and baseline patient characteristics.

The management of myelosuppression with the existing treatment armamentarium remains suboptimal, and an unmet need remains for a treatment that can minimize side effects by providing multilineage protection from cytotoxic damage, particularly among high-risk patients. In addition, no therapy protects from the myelosuppressive effects of chemotherapy before they occur.

Myelosuppression (including neutropenia, thrombocytopenia and anemia) symptoms include fatigue, weakened immune system, bleeding and/or bruising, and shortness of breath, in addition to pale skin, drowsiness, depression, tachycardia and dizziness. These have a negative impact on patients' daily lives, diminishing their ability to complete tasks at home and work, and to socialize. And there is a high concern particularly about fatigue, because fatigue is one of the three key issues impacting lymphoma patients, across the whole patient journey, persisting years after stopping treatments. CIN often isolates patients from family and friends, and means that they are unable to work or perform tasks of daily living but it also implies a considerable economic and humanistic burden, incurring substantial financial costs. Last but not least, CIN is associated with increased morbidity, mortality, and healthcare costs.

Patients who develop CIN may require hospitalization, with mean length of hospital stay ranging from 4.1 to 7.9 days. This increase in hospitalization and patient management has a large economic impact.

To manage CIN, physicians often dose-reduce or delay chemotherapy to allow for neutrophil recovery. Although this approach reduces the negative impact of chemotherapy, it also results in lower RDI and poorer clinical outcomes because patients are not receiving the optimal dose and frequency of chemotherapy to most effectively treat their disease. Newer agents to treat and/or prevent CIN may potentially change the treatment landscape for CIN in the future.

As the incidence of Chemotherapy-Induced Neutropenia (CIN) affects 10–78% to Lymphoma patients diagnosed with Non-Hodgkin subtypes, and considering the unmet need for better treatments for CIN, Lymphoma Coalition became interested in reviewing the *“ICER's Draft Scoping Document Novel Agents to Prevent Chemotherapy-Induced Neutropenia”*, aim to evaluate new agents recently developed for the treatment of CIN, as Trilaciclib and Plinabulin.

Considerations to COVID context

Issues relating to myelosuppression in patients with cancer are especially applicable in the context of COVID-19, as changes in hematologic parameters are common in infected patients, particularly in severe cases.

COVID-19 pandemic impacts on blood product supplies, with concerns regarding infection and social isolation potentially leading to a reduction in blood donations. Consequently, there is a need to consider additional measures to prevent and mitigate the consequences of myelosuppression and to facilitate continued administration of effective chemotherapy.

Comments to the Scoping Document Novel Agents to Prevent CIN

Novel Agents to Prevent Chemotherapy-Induced Neutropenia

Drug	Mechanism	Dose
Trilaciclib (Cosela™)	CDK 4/6 Inhibition	240 mg/m ² IV within 4 hours prior to chemotherapy
Plinabulin	Selective microtubule-binding agent	40 mg IV with chemotherapy

These are the two new agents targeted in the scoping document, which may be used in certain situations in place of or in conjunction with G-CSF.

- As CIN impacts also hematologic malignancies as NHL, the document should target “hematologist & oncologists” rather than oncologists only.
- We suggest to re-evaluate the population of focus for the review, limiting to RCOG 0 or 1 is not realistic. Many hematologic and cancer patients present ECOG 2. So the risks is that you would be leaving behind an important group of patients who are in risk of CIN. They may have access to normal or reduced dosis of Chemotherapy threatment, or mixed regimens, but higher ECOG status may lead to increased toxicity.
- When considering the patient-important outcomes, it will be key to define well the domains considered in quality of life, as this wording may be ambiguous. We would suggest to list the different parameters, especially those that match better where the impact of the CIN is notorious.
- Both agents reduced incidence of hospitalizations and reductions in the occurrences of severe/profound neutropenia, this is of special importance when considering the risks of healthcare-associated transmission of COVID-19, and COVID-19 complications associated with CIN.
- Trilaciclib results very effective to reduce the use of supportive care interventions, and myelosuppression related hospitalizations, while improving quality of life.
- Reasoning on the patient experience, is especially valuable that plinabulin showed a similar effect on CIN (compared with pegfilgrastim) but reducing in addition the incidence of thrombocytopenia; and resulting in less bone pain. The progress observed in quality of life

domains as global health status, symptom scales, and summary score, with additional improvements in fatigue, pain, and insomnia symptom scales may lead to better patient experience, which in our perspective must be considered.

- Regarding the comparators, we support the comparators proposed in the document.
- Improving communication between patients and oncologists, nurses, PAs, and other HCPs may result in more effective management of CIM-related symptoms and increase the likelihood of patients maintaining daily lives that are as close to normal as possible. Patients should be informed about expected side effects associated to the use of G-CSF, but it is not only essential to communicate to the patient but include these strategies in clinical practice guidelines and disseminate thru the clinicians and nurses' societies as the second ones (HNP) are best prepared to communicate with patients and carers.

Sandoz, A Novartis Division

Submitted VIA ELECTRONIC SUBMISSION at publiccomments@icer.org

September 14, 2021

Institute for Clinical and Economic Review
Two Liberty Square
Ninth Floor
Boston, MA 02109

RE: Draft Scoping Document

Dear Sir or Madam,

Sandoz, A Novartis division, is submitting this letter to the Institute for Clinical and Economic Review (ICER) in response to the Draft Scoping Document outlining the planned review of Novel Agents to Prevent Chemotherapy-Induced Neutropenia released on August 25, 2021.¹ While ICER's planned scope revolves around the evaluation of newer agents – trilaciclib and plinabulin – for chemotherapy-induced neutropenia (CIN), we would like remind you of the value of established therapies, specifically the granulocyte-colony stimulating factors (G-CSFs) pegfilgrastim and filgrastim along with their corresponding biosimilars.

The abundance of evidence has demonstrated that G-CSFs have dramatically improved outcomes and subsequently provide much value to patients receiving myelosuppressive chemotherapy.² One analysis estimated the total social value of growth factors in 2014 to be \$8.5 billion, owing to the ability to deliver higher effective chemotherapy doses, improvements in health-related quality of life, and reductions in febrile neutropenia (FN) hospitalizations, FN-related deaths, antibiotics, and indirect costs.³

However, in the draft scoping document, ICER states that the use of G-CSFs for primary prophylaxis in patients with a <20% FN risk is an example of a “low-value service.” This statement was originally written in the year 2012, and it must be recognized that this 20% threshold was lowered from 40% in 2005, based on both clinical and economic rationales.^{4,5}

Sandoz believes that with the availability of biosimilars and the rising costs of hospitalizations (as well as the diminishing availability of hospital beds given the COVID-19 pandemic), this statement should be revisited. For example, we demonstrated that the use of filgrastim-sndz as

¹ Institute for Clinical and Economic Review (ICER). Novel Agents to Prevent Chemotherapy-Induced Neutropenia: Draft Background and Scope. https://icer.org/wp-content/uploads/2021/08/ICER_Neutropenia_Draft_Scope_082521.pdf

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primary prophylaxis in patients receiving chemotherapy at intermediate-risk within three different tumor types is cost-effective compared to secondary prophylaxis at the \$50,000/QALY willingness-to-pay threshold.⁶ Given this information, we recommend that ICER expand the scope of the CIN review to include GCSF primary prophylaxis versus secondary prophylaxis in patients receiving myelosuppressive chemotherapy at various risk categories in the current era.

We want to express our appreciation to ICER for the opportunity to provide comments on the Draft Scoping Document. If any questions arise regarding our comments, please contact us.

Sincerely,

Edward Li, PharmD, MPH
Director, Health Economics & Outcomes Research
Sandoz

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