DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Chris Jewell, JD, MBA
Senior Vice President and General Counsel
Taiho Oncology, Inc.
101 Carnegie Center, Suite 101
Princeton, NJ 08540

RE: NDA 214801
LYTGOBI® (futibatinib) tablets, for oral use
MA 89

Dear Chris Jewell:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed the promotional communication, the "Efficacy Results" webpage[1] (webpage) on the LYTGOBI Healthcare Provider Branded Website (FUTI-PM-US-0024 v2)[2] (website) for LYTGOBI® (futibatinib) tablets, for oral use (Lytgobi) submitted by Taiho Oncology, Inc. (Taiho) under cover of Form FDA 2253.

The webpage makes false or misleading representations about the benefits of Lytgobi. Thus, the webpage misbrands Lytgobi within the meaning of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and makes its distribution violative. 21 U.S.C. 352(a), (n); 321(n); 331(a). *See* 21 CFR 202.1(e)(5). These violations are particularly concerning because the promotional communication makes misleading representations about the efficacy of Lytgobi in patients with previously treated, unresectable, locally advanced or metastatic intrahepatic cholangiocarcinoma (iCCA) harboring fibroblast growth factor receptor 2 (FGFR2) gene fusions or other rearrangements. Intrahepatic bile duct cancers have an estimated 5-year relative survival rate of 9%.[3] Unresectable, locally advanced or metastatic iCCA is a serious public health concern as this unresectable cancer cannot be removed completely by surgery and treatment for this condition involves serious risks.[4]

Background

Below are the indication and summary of the most serious and most common risks

[1] The "Efficacy Results" webpage is accessed from the "Efficacy & Safety" sub-navigation menu of the website: https://www.lytgobi.com/hcp/efficacy-and-safety/efficacy-results (last accessed March 19, 2025).
[2] The material ID referenced on the "Efficacy Results" webpage includes "v2."
[3] American Cancer Society: Survival Rates for Bile Duct Cancer. See: https://www.cancer.org/cancer/types/bile-duct-cancer/detection-diagnosis-staging/survival-by-stage.html (last accessed March 19, 2025).
[4] National Cancer Institute: What Is Bile Duct Cancer (Cholangiocarcinoma)? See: https://www.cancer.gov/types/liver/bile-duct-cancer (last accessed March 19, 2025).

associated with the use of Lytgobi.[5] According to the INDICATIONS AND USAGE section of the FDA-approved Prescribing Information (PI) (in pertinent part):

> LYTGOBI is indicated for the treatment of adult patients with previously treated, unresectable, locally advanced or metastatic intrahepatic cholangiocarcinoma harboring fibroblast growth factor receptor 2 (FGFR2) gene fusions or other rearrangements.
>
> This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Lytgobi was approved under the accelerated approval pathway. This pathway can allow for earlier approval of drugs intended to treat serious conditions and fill an unmet medical need. Accelerated approval is based on an effect on a surrogate or intermediate clinical endpoint that is thought to be reasonably likely to predict clinical benefit, rather than on a direct measurement of clinical benefit. FDA has required sponsors of drugs approved under the accelerated approval pathway, including Lytgobi, to conduct a confirmatory trial to verify and describe the clinical benefit of the drug.[6]

The PI for Lytgobi includes warnings and precautions regarding ocular toxicity, hyperphosphatemia and soft tissue mineralization, and embryo-fetal toxicity. The most common adverse reactions reported with use of Lytgobi include nail toxicity, musculoskeletal pain, constipation, diarrhea, fatigue, dry mouth, alopecia, stomatitis, abdominal pain, dry skin, arthralgia, dysgeusia, dry eye, nausea, decreased appetite, urinary tract infection, palmar-plantar erythrodysesthesia syndrome, and vomiting.

Prior Communications

OPDP notes that our advisory comments dated December 7, 2022, to Taiho addressed draft claims and presentations for Lytgobi (b) (4) [redacted] OPDP is concerned that Taiho appears to be promoting Lytgobi using similar claims and presentations in a misleading manner.

[5] This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional communication(s) cited in this letter.
[6] We note that the confirmatory trial, a randomized phase 2 trial, for Lytgobi, TAS-120-205, is currently ongoing; however, this study has not been completed. See: https://clinicaltrials.gov/study/NCT05727176.

False or Misleading Benefit Presentation

Prescription drug advertisements and labeling (promotional communications) misbrand a drug if they are false or misleading with respect to benefits. The determination of whether a promotional communication is misleading includes, among other things, not only representations made or suggested in the promotional communication, but also the extent to which the promotional communication fails to reveal facts material in light of the representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the promotional communication.

The "Efficacy Results" webpage, under the "Efficacy & Safety" sub-navigation menu of the website for Lytgobi, includes the following in conjunction with efficacy representations regarding PFS and OS (in pertinent part, emphasis original, footnotes omitted):

- Presentation of a Kaplan-Meier estimate graph of PFS titled, "Progression-free survival (PFS)," showing "Progression-free Survival (%)" on the y-axis and "Months" on the x-axis
    - "**Median [PFS], 9.0 mo (95% CI: 6.9, 13.1)**"
    - "Median follow-up at time of data cutoff was 17.1 months"
- Presentation of a Kaplan-Meier estimate graph of OS titled, "Overall survival (OS)," showing "Overall Survival (%)" on the y-axis and "Months" on the x-axis
    - "**Median [OS], 21.7 mo (95% CI: 14.5, Not Reached)**"
    - "At the time of data cutoff: Median follow-up was 17.1 months; the OS data were not mature; during the study, 40 patients (39%) died following treatment discontinuation with the majority (90%) dying from disease progression."

Similarly, the "Efficacy Results" webpage includes the following representations under the "Supplementary results" bolded header (in pertinent part, emphasis original):

- "**Efficacy results at extended follow-up**"
- "At a nonprespecified follow-up analysis conducted 8 months after the primary analysis (data cutoff, May 29, 2021; median follow-up, 25.0 months), efficacy in the overall study population was maintained with:

  . . .

    - "median PFS of 8.9 months"
    - "median OS of 20.0 months"

As a reference for these representations, you cite a publication and two abstract presentations from Goyal, et al, which include results from the FOENIX-CCA2 trial. [7,8,9] These parts of the webpage misbrand Lytgobi by misleadingly suggesting that FOENIX-CCA2 provided interpretable results regarding the effects of Lytgobi on PFS and OS endpoints, even though the design of the FOENIX-CCA2 study was not capable of establishing improvement on time-to-event efficacy endpoints such as OS or PFS. Specifically, because FOENIX-CCA2 was designed as a single-arm trial (i.e., with no comparator arm), and PFS and OS are time-to-event efficacy endpoints, the reported PFS and OS results are uninterpretable; absent an appropriate comparator, it is not possible to determine if the observed effect is attributable to Lytgobi or to other factor(s), such as the natural history of the disease.

We acknowledge that the following text appears above the PFS and OS presentations, under the bolded heading “FOENIX-CAA2: Additional endpoints” (in pertinent part, emphasis original, footnotes omitted):

- Due to potential variability in the natural history of the disease, a single-arm study may not adequately characterize these time-to-event endpoints and the results may not be interpretable

- **This data presentation is neither intended to draw conclusions regarding the efficacy of LYTGOBI nor to imply that there is a treatment effect of LYTGOBI on these time-to-event endpoints and the results should be interpreted with caution**

In addition, after the representations regarding efficacy results at extended follow-up, the following text appears in conjunction with the PFS and OS presentations: “The extended follow-up data were collected after the primary analysis and are descriptive in nature, and results should be interpreted with caution.” However, including these statements in Lytgobi promotional communications, along with misleading representations about Lytgobi’s efficacy (i.e., PFS and OS results from FOENIX-CCA2), does not render the promotional communication nonmisleading in light of the issues with FOENIX-CCA2 (explained above) that make the study incapable of supporting representations or suggestions that these results are attributable to the effect of Lytgobi.

The “Efficacy Results” webpage also includes the following efficacy presentations regarding DCR (in pertinent part, emphasis original, footnotes omitted):

- “**Disease control rate (DCR) (n=103)**”

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[7] Goyal L, Meric-Bernstam F, Hollebecque A, et al. Futibatinib for FGFR2-Rearranged Intrahepatic Cholangiocarcinoma. *N Engl J Med*. 2023;388(3):228-239.
[8] Goyal L, Meric-Bernstam F, Hollebecque A, et al. Primary results of phase 2 FOENIX-CCA2: the irreversible FGFR1–4 inhibitor futibatinib in intrahepatic cholangiocarcinoma with FGFR2 fusions/rearrangements. Abstract presented at: American Association for Cancer Research Annual Meeting; April 10-15, 2021, and May 17-21, 2021. Abstract CT010.
[9] Goyal L, Meric-Bernstam F, Hollebecque A, et al. Updated results of the FOENIX-CCA2 trial: Efficacy and safety of futibatinib in intrahepatic cholangiocarcinoma (iCCA) harboring FGFR2 fusions/rearrangements. Abstract presented at ASCO Annual Meeting 2022. Abstract 4009. J Clin Oncol. 2022;40(16 suppl).

- "**83% DCR (95% CI: 74, 89)**" depicted inside of a pie chart that includes shading to show the 83% DCR

Similarly, the following representation regarding efficacy results at extended follow-up is presented on the "Efficacy Results" webpage: "At a nonprespecified follow-up analysis conducted 8 months after the primary analysis (data cutoff, May 29, 2021; median follow-up, 25.0 months), efficacy in the overall study population was maintained with … DCR of 82.5%." As provided on this webpage, DCR is defined as "the sum of complete response, partial response, and stable disease." These presentations make these promotional communications misleading by suggesting that Lytgobi improves DCR in patients with locally advanced or metastatic iCCA based on a composite of complete response (CR), partial response (PR), and stable disease (SD) when the study from which the presentations were drawn could not demonstrate this result. Lytgobi was approved based on an effect shown on overall response rate (ORR) and duration of response endpoints in FOENIX-CCA2, a single-arm trial. In FOENIX-CCA2, the endpoint of ORR was comprised only of PR + CR, as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1.[10] Because FOENIX-CCA2 was designed as a single arm trial, the study did not establish that the SD result was attributable to the effect of the drug; for example, the result may instead reflect the natural history of the disease. An assessment of delay in time to disease progression in patients treated with Lytgobi (i.e., an assessment of SD) would need to be based on the results of a randomized controlled trial.

You cite the same publication and presentations from Goyal, et al, that are referenced above in support of these representations.[7,8,9] These references include results from FOENIX-CCA2. However, it is misleading to include in promotional communications representations or suggestions that rely on a study or studies whose design is not capable of supporting such representations or suggestions. Here, as already noted, since FOENIX-CCA2 was a *single-arm trial*, it is not known whether the data on SD are attributable to treatment with Lytgobi. Consequently, the DCR calculations, which are based on a composite that includes SD data, are not supported by the data cited. In addition to the disclosures of the study's limitations noted previously, we acknowledge that the following text appears in conjunction with the DCR presentations regarding the results from the primary analysis: "FOENIX-CCA2 was a single-arm study. In this setting, the DCR results may reflect the natural history of cholangiocarcinoma in an individual patient, rather than the direct effect of treatment." In addition, we acknowledge that the following text appears with the "efficacy results at extended follow-up" representation: "The extended follow-up data were collected after the primary analysis and are descriptive in nature, and results should be interpreted with caution." However, for the reasons discussed above, these promotional communications make misleading representations or suggestions about the efficacy of Lytgobi through the presentation of DCR calculations that include SD and that are based on the FOENIX-CCA2 study, which, as a single-arm trial, is not capable of supporting such representations or

[10] Response was measured using the Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1., which defines the evaluation of target lesions as the following: Complete Response (CR): Disappearance of all target lesions. Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. See: https://ctep.cancer.gov/protocoldevelopment/docs/recist_guideline.pdf.

suggestions. The disclosures of the study's limitations (noted above) in this promotional communication do not correct or mitigate the misleading representations or suggestions of the presentation.

Conclusion and Requested Action

For the reasons discussed above, the webpage misbrands Lytgobi within the meaning of the FD&C Act and makes its distribution violative. 21 U.S.C. 352(a), (n); 321(n); 331(a). *See* 21 CFR 202.1(e)(5).

This letter notifies you of our concerns and provides you with an opportunity to address them. OPDP requests that Taiho cease any violations of the FD&C Act. Please submit a written response to this letter within 15 working days from the date of receipt, addressing the concerns described in this letter, listing all promotional communications (with the 2253 submission date) for Lytgobi that contain representations like those described above, and explaining your plan for the timely discontinuation of such communications, or for ceasing distribution of Lytgobi.

If you believe that your products are not in violation of the FD&C Act, please include in your submission to us your reasoning and any supporting information for our consideration within 15 working days from the date of receipt of this letter.

The concerns discussed in this letter do not necessarily constitute an exhaustive list of potential violations. It is your responsibility to ensure compliance with each applicable requirement of the FD&C Act and FDA implementing regulations.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266**. A courtesy copy can be sent by facsimile to (301) 847-8444. Please refer to MA 89 in addition to the NDA number in all future correspondence relating to this particular matter. All correspondence should include a subject line that clearly identifies the submission as a Response to Untitled Letter. You are encouraged, but not required, to submit your response in eCTD format. All correspondence submitted in response to this letter should be placed under eCTD Heading 1.15.1.6.

Additionally, the response submission should be coded as an Amendment to eCTD Sequence 5046 under NDA 214801. Questions related to the submission of your response letter should be emailed to the OPDP RPM at CDER-OPDP-RPM@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Rebecca Falter, PharmD, BCACP
Regulatory Review Officer
Division of Advertising & Promotion Review 1
Office of Prescription Drug Promotion

{See appended electronic signature page}

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/s/

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