Adding Real-World Evidence to a Totality of Evidence Approach for Evaluating Marketed Product Effectiveness

December 19, 2019
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APPENDIX A. WORKSHOP PARTICIPANTS

Improving RWE Study Credibility and its Role in Totality of Evidence
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June 20, 2019

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APPENDIX B. PREVIOUS DUKE-MARGOLIS WORK ON RWD AND RWE

A Framework for Regulatory Use of Real-World Evidence
September 15, 2017
Secures distinct definitions for what constitutes RWD and RWE, the considerations that should guide the development of RWD that is fit for regulatory purposes, and high-priority opportunities to improve such development and use.

Characterizing RWD Quality and Relevancy for Regulatory Purposes
October 3, 2018
Provides an overview of the data extraction process and identifies potential challenges for regulators in assessing the underlying appropriateness of the RWD source for the given regulatory question of interest.

Determining Real-World Data’s Fitness for Use and the Role of Reliability
September 26, 2019
Examines the key components of RWD fitness for use considerations and identifies principles for developing a minimum set of reliability checks.

Understanding the Need for Non-Interventional Studies Using Secondary Data to Generate Real-World Evidence for Regulatory Decision Making, and Demonstrating Their Credibility
November 29, 2019
Provides guidance on when conducting interventional RWE studies may not be possible and how to demonstrate credibility in the causal inference made by non-interventional studies using secondary data (observational studies).

Adding Real-World Evidence to a Totality of Evidence Approach for Evaluating Marketed Product Effectiveness
December 20, 2019
Explores how RWE studies can support regulatory decision-making based on a totality of evidence approach.
### APPENDIX C. EXAMPLES OF DRUG APPROVALS AND LABELING CHANGES USING EVIDENCE GENERATED FROM NON-TRADITIONAL STUDY DESIGNS

#### Table C1. RWE studies

<table>
<thead>
<tr>
<th>PRODUCT</th>
<th>SPONSOR</th>
<th>DISEASE</th>
<th>STUDY DESIGN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bavencio® (avelumab)15-17</td>
<td>Pfizer and Merck KGaA</td>
<td>Metastatic merkel cell carcinoma</td>
<td>1. Open-label single-arm multicenter trial</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. RWE-generated historical control as benchmark</td>
</tr>
<tr>
<td>Blincyto® (blinatumomab)18-21</td>
<td>Amgen</td>
<td>B-cell precursor acute lymphoblastic leukemia</td>
<td>1. Open-label single-arm multicenter trial</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. RWE-generated historical control</td>
</tr>
<tr>
<td>Brineura® (cerliponase alfa)22-24</td>
<td>Biomarin</td>
<td>Infantile batten disease</td>
<td>1. Non-randomized single-arm dose-escalation study</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. Non-randomized comparison with natural history cohort</td>
</tr>
<tr>
<td>Carbaglu® (carglumic acid)25,26</td>
<td>Recordati Rare Diseases Inc.</td>
<td>Hyperammonemia</td>
<td>Retrospective unblinded uncontrolled case series</td>
</tr>
<tr>
<td>Cordarone® (amiodarone hydrochloride) tablets27,28</td>
<td>Sanofi</td>
<td>Arrhythmia</td>
<td>Retrospective open-label self-controlled study</td>
</tr>
<tr>
<td>Ibrance® (palbociclib)29-33</td>
<td>Pfizer</td>
<td>Male breast cancer</td>
<td>Retrospective cohort study using EHR data, insurance billing data, and postmarketing studies</td>
</tr>
<tr>
<td>Intravenous ganciclovir34,35</td>
<td>Exela Pharma Sciences</td>
<td>Acquired immunodeficiency virus syndrome (AIDS) and cytomegalovirus (CMV) retinitis</td>
<td>Retrospective non-randomized study</td>
</tr>
<tr>
<td>Luthathera® (lutetium Lu 177 dotatate)36,37</td>
<td>Advanced Accelerator Applications, a Novartis company</td>
<td>Somatostatin receptor (SSTR) positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs)</td>
<td>1. Randomized open-label, active-controlled multicenter trial</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. Retrospective study</td>
</tr>
<tr>
<td>Omegaven® (fish oil triglycerides)38,39</td>
<td>Fresenius Kabi</td>
<td>Parenteral nutrition-associated cholestasis</td>
<td>1. Open-label single-center trial</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. Open-label single-center trial</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3. Historical control</td>
</tr>
<tr>
<td>Tepadina® (thiotepa)40,41</td>
<td>Adienne SA</td>
<td>Pediatric class 3 beta-thalassemia</td>
<td>Retrospective observational trial</td>
</tr>
<tr>
<td>Yescarta® (axicabtagene ciloleucel)42-44</td>
<td>Kite, a Gilead company</td>
<td>Diffuse large B-cell lymphoma</td>
<td>1. Open-label single-arm multicenter trial</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. Retrospective analysis of patients receiving standard of care as benchmark</td>
</tr>
<tr>
<td>Zostavax® (zoster vaccine live)45,46</td>
<td>Merck</td>
<td>Herpes zoster (shingles)</td>
<td>1. Randomized double-blind placebo-controlled trial (ages 50–59)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. Randomized double-blind placebo-controlled trial (age &gt;60)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3. Prospective observational cohort study</td>
</tr>
</tbody>
</table>
Table C1. RWE studies (continued)

<table>
<thead>
<tr>
<th>PRODUCT</th>
<th>SPONSOR</th>
<th>DISEASE</th>
<th>STUDY DESIGN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Savaysa® (edoxaban)47,48</td>
<td>Daiichi Sankyo, Inc.</td>
<td>Atrial fibrillation</td>
<td>Randomized double-blind multinational non-inferiority study</td>
</tr>
<tr>
<td>Invega Sustenna® (paliperidone palmitate)49,50</td>
<td>Janssen</td>
<td>Schizophrenia, schizoaffective disorder</td>
<td>Prospective randomized open-label active-controlled parallel-group trial</td>
</tr>
<tr>
<td>Inactivated polio vaccine51-53</td>
<td>National Foundation for Infantile Paralysis (March of Dimes)</td>
<td>Polio</td>
<td>Randomized blinded placebo-controlled trial with additional observed controls</td>
</tr>
</tbody>
</table>

Table C2. Approvals based on <2 adequate and well-controlled studies

<table>
<thead>
<tr>
<th>PRODUCT</th>
<th>SPONSOR</th>
<th>DISEASE</th>
<th>STUDY DESIGN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altace® (ramipril)54,55</td>
<td>King Pharmaceuticals, Inc.</td>
<td>Hypertension, heart failure</td>
<td>Randomized double-blind placebo-controlled multicenter multinational trial</td>
</tr>
<tr>
<td>Capoten® (captopril)55</td>
<td>Bristol Myers Squibb</td>
<td>Hypertension, heart failure</td>
<td>Randomized double-blind placebo-controlled trial</td>
</tr>
<tr>
<td>Darzalex® (daratumumab)56,57</td>
<td>Janssen</td>
<td>Multiple myeloma</td>
<td>1. Open-label single-arm trial (phase II)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. Open-label dose expansion dose-escalation trial</td>
</tr>
<tr>
<td>Keytruda® (pembrolizumab)58,59</td>
<td>Merck</td>
<td>Metastatic melanoma</td>
<td>Randomized open-label dose-ranging multicenter cohort from a randomized open-label dose-finding activity-estimating safety and tolerability trial</td>
</tr>
<tr>
<td>Mavik® (trandolopril)55,60</td>
<td>Roussel–Uclaf and Knoll Pharmaceuticals</td>
<td>Hypertension, heart failure</td>
<td>Randomized double-blind placebo-controlled trial</td>
</tr>
<tr>
<td>Vasotec® (enalapril)55</td>
<td>Merck</td>
<td>Hypertension, heart failure</td>
<td>Randomized double-blind placebo-controlled trial</td>
</tr>
<tr>
<td>Zestri® (lisinopril)55,61</td>
<td>Zeneca Pharmaceutical</td>
<td>Hypertension, heart failure</td>
<td>Randomized controlled multicenter open trial</td>
</tr>
<tr>
<td>Zykadia® (ceritinib)62,63</td>
<td>Novartis</td>
<td>Metastatic non-small cell lung cancer</td>
<td>Open-label single-arm multicenter trial</td>
</tr>
</tbody>
</table>
### APPENDIX D. STUDY DESIGN EXAMPLES

Table D1. Examples of interventional study designs that historically have contributed to evidence packages for labeling changes

<table>
<thead>
<tr>
<th>STUDY DESIGN</th>
<th>DEFINITION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-arm</td>
<td>All trial participants received the experimental treatment&lt;sup&gt;64&lt;/sup&gt;</td>
</tr>
<tr>
<td>Open-label</td>
<td>Trial participant and researcher knew which treatment was assigned to the participant&lt;sup&gt;65&lt;/sup&gt;</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>A statistical analysis of combined results from multiple studies&lt;sup&gt;66&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
APPENDIX E. CLINICAL CONTEXT CONSIDERATIONS

Understanding of the Disease
Understanding of the disease includes disease biology characteristics for the specific patient population that will be studied, among other factors.

Treatment Alternatives
Identifying challenges with current treatment alternatives and their status, inclusive of the effectiveness and safety profile, and opportunities for the new therapy to address these challenges may determine the degree of unmet need and value of studying the new therapy. When alternative therapies exist, considering if there is clinical equipoise, a requirement for conducting interventional studies, is important.

Unmet need: A condition in which the available therapies do not sufficiently address the diagnosis or treatment or when an available therapy does not exist. Unmet need can refer to an immediate need to treat a specific condition or population or a long-term societal need.67

Understanding of the Therapy
To compare the new therapy to existing treatment alternatives or to address an unmet need, a clear understanding of the intended therapeutic effect on the population of interest is necessary. The interplay between the therapy and the disease provides information on the impact on patients and likelihood of treatment success, including not only safety and effectiveness but also quality-of-life considerations.

Patient Perspective
Considering the patient’s perspective is necessary because therapies can affect patients in unique ways. Considering outcomes, preferences, and treatment estimates that are most important among sub-populations is especially important for diseases that impact broad patient populations. Furthermore, different populations may be studied in RCTs compared to RWE studies, thereby potentially affecting the generalizability.

Provider Perspective
Because a provider will likely determine which drug to prescribe to each patient, provider perspective, including behavior and approach to clinical care, can also have a significant impact on the RWE study.
Subpart D — FDA Action on Applications and Abbreviated Applications

Sec. 314.126 Adequate and well-controlled studies.

(a) The purpose of conducting clinical investigations of a drug is to distinguish the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation. The characteristics described in paragraph (b) of this section have been developed over a period of years and are recognized by the scientific community as the essentials of an adequate and well-controlled clinical investigation. The Food and Drug Administration considers these characteristics in determining whether an investigation is adequate and well-controlled for purposes of section 505 of the act. Reports of adequate and well-controlled investigations provide the primary basis for determining whether there is “substantial evidence” to support the claims of effectiveness for new drugs. Therefore, the study report should provide sufficient details of study design, conduct, and analysis to allow critical evaluation and a determination of whether the characteristics of an adequate and well-controlled study are present.

(b) An adequate and well-controlled study has the following characteristics:

(1) There is a clear statement of the objectives of the investigation and a summary of the proposed or actual methods of analysis in the protocol for the study and in the report of its results. In addition, the protocol should contain a description of the proposed methods of analysis, and the study report should contain a description of the methods of analysis ultimately used. If the protocol does not contain a description of the proposed methods of analysis, the study report should describe how the methods used were selected.

(2) The study uses a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect. The protocol for the study and report of results should describe the study design precisely; for example, duration of treatment periods, whether treatments are parallel, sequential, or crossover, and whether the sample size is predetermined or based upon some interim analysis. Generally, the following types of control are recognized:

(i) Placebo concurrent control. The test drug is compared with an inactive preparation designed to resemble the test drug as far as possible. A placebo-controlled study may include additional treatment groups, such as an active treatment control or a dose-comparison control, and usually includes randomization and blinding of patients or investigators, or both.
(ii) **Dose-comparison concurrent control.** At least two doses of the drug are compared. A dose-comparison study may include additional treatment groups, such as placebo control or active control. Dose-comparison trials usually include randomization and blinding of patients or investigators, or both.

(iii) **No treatment concurrent control.** Where objective measurements of effectiveness are available and placebo effect is negligible, the test drug is compared with no treatment. No treatment concurrent control trials usually include randomization.

(iv) **Active treatment concurrent control.** The test drug is compared with known effective therapy; for example, where the condition treated is such that administration of placebo or no treatment would be contrary to the interest of the patient. An active treatment study may include additional treatment groups, however, such as a placebo control or a dose-comparison control. Active treatment trials usually include randomization and blinding of patients or investigators, or both. If the intent of the trial is to show similarity of the test and control drugs, the report of the study should assess the ability of the study to have detected a difference between treatments. Similarity of test drug and active control can mean either that both drugs were effective or that neither was effective. The analysis of the study should explain why the drugs should be considered effective in the study, for example, by reference to results in previous placebo-controlled studies of the active control drug.

(v) **Historical control.** The results of treatment with the test drug are compared with experience historically derived from the adequately documented natural history of the disease or condition, or from the results of active treatment, in comparable patients or populations. Because historical control populations usually cannot be as well assessed with respect to pertinent variables as can concurrent control populations, historical control designs are usually reserved for special circumstances. Examples include studies of diseases with high and predictable mortality (for example, certain malignancies) and studies in which the effect of the drug is self-evident (general anesthetics, drug metabolism).

(3) The method of selection of subjects provides adequate assurance that they have the disease or condition being studied, or evidence of susceptibility and exposure to the condition against which prophylaxis is directed.

(4) The method of assigning patients to treatment and control groups minimizes bias and is intended to assure comparability of the groups with respect to pertinent variables such as age, sex, severity of disease, duration of disease, and use of drugs or therapy other than the test drug. The protocol for the study and the report of its results should describe how subjects were assigned to groups. Ordinarily, in a concurrently controlled study, assignment is by randomization, with or without stratification.

(5) Adequate measures are taken to minimize bias on the part of the subjects, observers, and analysts of the data. The protocol and report of the study should describe the procedures used to accomplish this, such as blinding.
(6) The methods of assessment of subjects’ response are well-defined and reliable. The protocol for the study and the report of results should explain the variables measured, the methods of observation, and criteria used to assess response.

(7) There is an analysis of the results of the study adequate to assess the effects of the drug. The report of the study should describe the results and the analytic methods used to evaluate them, including any appropriate statistical methods. The analysis should assess, among other things, the comparability of test and control groups with respect to pertinent variables, and the effects of any interim data analyses performed.

(c) The Director of the Center for Drug Evaluation and Research may, on the Director’s own initiative or on the petition of an interested person, waive in whole or in part any of the criteria in paragraph (b) of this section with respect to a specific clinical investigation, either prior to the investigation or in the evaluation of a completed study. A petition for a waiver is required to set forth clearly and concisely the specific criteria from which waiver is sought, why the criteria are not reasonably applicable to the particular clinical investigation, what alternative procedures, if any, are to be, or have been employed, and what results have been obtained. The petition is also required to state why the clinical investigations so conducted will yield, or have yielded, substantial evidence of effectiveness, notwithstanding nonconformance with the criteria for which waiver is requested.

(d) For an investigation to be considered adequate for approval of a new drug, it is required that the test drug be standardized as to identity, strength, quality, purity, and dosage form to give significance to the results of the investigation.

(e) Uncontrolled studies or partially controlled studies are not acceptable as the sole basis for the approval of claims of effectiveness. Such studies carefully conducted and documented, may provide corroborative support of well-controlled studies regarding efficacy and may yield valuable data regarding safety of the test drug. Such studies will be considered on their merits in the light of the principles listed here, with the exception of the requirement for the comparison of the treated subjects with controls. Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered.

APPENDIX G. IBRANCE® CASE STUDY

DISCLAIMER: The following evaluation of the Ibrance® approval process is an interpretation of the evidence conducted by this Center. This interpretation does not represent the opinions of the sponsors, manufacturers, or any third parties involved in the regulatory submission, nor does it represent the opinions of the FDA.

Ibrance® (Pfizer)

Regulatory Context

In 2019, Ibrance® (palbociclib) was approved to treat HR+ and HER2- advanced or metastatic breast cancer (BC) in combination with an aromatase inhibitor as an initial endocrine-based therapy in postmenopausal women or men, or with fulvestrant in patients with disease progression following endocrine therapy.\(^{29,30}\) Previously approved for women only (Figure G1), this labeling change for Ibrance® included men as a new population.

Clinical Context

Disease Background

Male breast cancer is extremely rare. Only 2,670 new cases of invasive breast cancer and 500 deaths from metastatic breast cancer in men are expected in 2019.\(^{69}\) Because the condition is so rare, a randomized trial is likely not possible, increasing the need to rely on RWE. Preclinical studies determined that the biology of the disease is similar in men and women; therefore, the proximity to the original indication was close. Additional clinical context information can be found in Table G1.
Current Therapies and Level of Unmet Need

There is a high unmet need for additional research on therapies for treating breast cancer in men. Because male breast cancer is rare (consisting of 1% of breast cancer cases), the majority of breast cancer research is performed in women. Additionally, few therapies are approved for men with breast cancer, leading to off-label prescribing of products approved for women and potentially contributing to treatment access issues. While the National Comprehensive Cancer Network (NCCN) Compendium generally recommends that male breast cancer patients receive the same treatments as female breast cancer patients, it also lists specific recommendations for male patients in terms of genetic counseling and surgical interventions highlighting differences in treatment considerations between men and women.70

Proposed Therapy

The therapy is an oral inhibitor of cyclin-dependent kinases (CDKs) 4 and 6. CDKs 4 and 6 are regulators of the cell cycle that trigger tumor cell progression.31,71

Patient and Provider Perspectives

Because breast cancer often affects women, men with breast cancer often face stigma from having a disease that may be perceived as a woman’s disease.72 Some men with breast cancer feel as if they are infiltrating women’s spaces. These men do not feel like part of the breast cancer community at clinics and rehabilitation centers, which can contribute to reduced access.72 Some clinics with gynecologists who treat breast cancer will not take male patients due to anticipated billing issues.72 The stigma surrounding breast cancer might also lead to the provider assuming that the patient is a woman, which can contribute to feelings of isolation in male breast cancer patients.72 Perceptions of the disease might also make providers less likely to diagnose breast cancer in men because it is so rare.

Evidence

Prior Evidence

This approval was based on prior evidence, including two randomized pivotal trials across the PALOMA program as well as additional evidence, including clinical pharmacology and non-clinical toxicology studies to support the biological plausibility.29 Additional information about the clinical trials can be found in Table G2.

New Evidence: Strengths and Limitations

New evidence to support this labeling change was obtained from postmarketing safety report data, insurance billing data, and electronic health record (EHR) data, and demonstrated clinical benefit for use in men.73 Additionally, the safety profile for use of ibrance® in men was found to be consistent with the safety profile for its use in women.74 Additional information about the studies can be found in Table G2.

*Compendia, resources to guide use of a drug after it has been prescribed off label, contain recommendations for the treatment of oncology patients.
Regulatory Decision

The labeling change to include men as a new population was largely based on prior evidence generated from the PALOMA trials and was supported by the RWE studies. In the approval package for Ibrance®, FDA states, “The effectiveness of palbociclib is expected to be the same in both women and men based on the mechanism of action for palbociclib. Given the extensive established efficacy and safety of the use of palbociclib in women observed in randomized clinical trials, the additional EHR data provided in this application for the use in men, modest as it is, does support the expansion of the palbociclib indication to provide for the treatment of men with metastatic breast cancer.” This supplemental application was novel in that all new evidence included was from RWD sources.

Table G1. Clinical context for Ibrance® approval in males

<table>
<thead>
<tr>
<th>DISEASE59</th>
<th>TREATMENT ALTERNATIVES</th>
<th>THERAPY</th>
<th>PATIENT PERSPECTIVE72</th>
<th>PROVIDER PERSPECTIVE72</th>
</tr>
</thead>
</table>
| • Biologically similar in men and women  
• Expected new cases in 2019: 2,670  
• Expected deaths in 2019: 500 | Limited treatment options | Oral inhibitor of CDKs 4 and 611,21 | • Unmet need  
• Stigma  
• Access to care | • Stigma  
• Perception of disease |

Table G2. Prior evidence and RWE for Ibrance® approval in males

<table>
<thead>
<tr>
<th>PRIOR EVIDENCE29</th>
<th>RWE73</th>
</tr>
</thead>
</table>
| • PALOMA-2 RCT  
  – Study design: randomized double-blind parallel-group multicenter trial  
  – Population: postmenopausal women with ER+, HER2- advanced or metastatic breast cancer  
  – Intervention: Ibrance® in combination with letrozole versus a placebo with letrozole  
  – Primary outcome: investigator-assessed progression-free survival evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) | • Postmarketing reports, insurance billing data, and EHR data sourced from:  
  – IQVIA insurance database  
  – Flatiron Health breast cancer database  
  – Pfizer global safety database |
| • PALOMA-3 RCT  
  – Study design: randomized double-blind parallel-group multicenter trial  
  – Population: women with HR+, HER2- advanced or metastatic breast cancer with disease progression after previous endocrine therapy  
  – Intervention: Ibrance® in combination with fulvestrant versus placebo in combination with fulvestrant  
  – Primary outcome: progression-free survival evaluated according to RECIST | |
| • Clinical pharmacology studies  
• Non-clinical toxicology studies | |
APPENDIX H. INVEGA SUSTENNA® CASE STUDY

DISCLAIMER: The following evaluation of the Invega Sustenna® approval process is an interpretation of the evidence conducted by this Center. This interpretation does not represent the opinions of the sponsors, manufacturers, or any third parties involved in the regulatory submission, nor does it represent the opinions of the FDA.

Invega Sustenna® (Janssen)

Regulatory Context
Invega Sustenna® (paliperidone palmitate) was approved first as an oral tablet, then as a long-acting injectable (LAI) antipsychotic (Figure H1).* In 2018, Invega Sustenna® was approved for a labeling change to include information comparing a long-term monotherapy treatment versus an oral antipsychotic therapy. Specifically, Invega Sustenna® was studied in a broader population including adults with schizophrenia who had recent incarcerations and largely included adults with substance abuse issues. Traditionally, these populations are not included in clinical trials, even though they represent a significant number of schizophrenia patients. This trial sought to increase relevancy by including a more representative population and using a real-world assessment of benefit, particularly given the challenges with adherence to treatment in these populations.

* Invega Sustenna® is indicated to treat both schizophrenia and schizoaffective disorder. It is the only once-monthly monotherapy LAI approved for schizoaffective disorder.

Figure H1. Labeling timeline for Invega Sustenna®
Clinical Context

Disease Background

Schizophrenia prevalence is approximately equal in men and women and occurs in about 1.1% of people in the United States. True prevalence of schizophrenia can be difficult to determine due to misdiagnosis and conflation with other mental disorders. DSM-5 characterizes schizophrenia as a spectrum with presence of two or more of the following symptoms within a month: delusions, hallucinations, disorganized speech (such as frequent derailment or incoherence), grossly disorganized or catatonic behavior, and negative symptoms (diminished emotional expression or avolition). For diagnosis, at least one of the symptoms exhibited must be delusions, hallucinations, or disorganized speech.

Schizoaffective disorder consists of an uninterrupted period of illness of schizophrenia symptoms in conjunction with a major depressive or manic mood episode. Diagnosis of schizophrenia and schizoaffective disorder are also evaluated in terms of additional criteria, outlined in DSM-5. Additional clinical context information can be found in Table H1.

Current Therapies and Level of Unmet Need

Pharmaceutical treatment options for people with schizophrenia include first- and second-generation antipsychotics, clozapine, mood stabilizers, combination therapies, and LAIs.

Proposed Therapy

Paliperidone palmitate hydrolyzes over time to paliperidone, which is a centrally active antagonist of the dopamine type 2 receptors and serotonin type 2 receptors.

Patient and Provider Perspectives

Provider perspective can often overshadow patient perspective in this case, with treatment decisions made without patient or caregiver input 67% of the time. Patients with less severe mental impairment are more likely to be a part of treatment decisions, and some providers emphasized that patients should have treatment autonomy. The most common reason for accepting an LAI antipsychotic was a benefit to adherence, which can include the convenience of taking the medication once or a few times per month rather than daily. Patients refused LAIs due to fear of needles, a lack of understanding of the disease or treatment option, the requirement that the drug be received at a site, and the lack of a guarantee of effectiveness of the drug. If a patient was resistant to trying an LAI, some providers ceased discussion in order to preserve the relationship with the patient or for fear of coercing the patient into trying a particular treatment. Providers expressed concerns over the side effects of LAIs and that patients cannot be immediately taken off the therapy if they experience a negative reaction. Providers recognized the adherence benefits associated with prescribing LAIs rather than oral antipsychotics, as adherence is a predictor of recovery for schizophrenia patients.
Evidence

Prior Evidence

Prior evidence was based on four short-term RCTs in patients with schizophrenia and one long-term, double-blind, placebo-controlled randomized withdrawal trial in patients with schizoaffective disorder. Additional information about the clinical trials can be found in Table H2.

New Evidence: Strengths and Limitations

New evidence consisted of the Paliperidone Palmitate Research in Demonstrating Effectiveness (PRIDE) trial, a randomized pragmatic trial in people with schizophrenia with recent incarceration. To increase this study’s pragmatism, researchers recruited non-traditional trial patients from homeless shelters, soup kitchens, jail-release programs, and jail-diversion programs. In this study, patients were randomized to a flexibly dosed monthly injection of Invega Sustenna® or a flexibly dosed oral antipsychotic. Researchers found that Invega Sustenna® delayed treatment failure when compared to oral antipsychotics. Additional information about the studies can be found in Table H2.

Regulatory Decision

The labeling change provided real-world clinical context about a broader population in the clinical studies section of the label. This population would not have been feasible to study in an RCT. Through a totality of evidence approach, the RWE study contributed evidence that a once-monthly LAI monotherapy was effective compared to a daily oral antipsychotic among schizophrenia patients with a broad inclusion criteria.

Table H1. Clinical context for including new evidence in the clinical studies section of the label for Invega Sustenna®

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>TREATMENT ALTERNATIVES75</th>
<th>THERAPY</th>
<th>PATIENT PERSPECTIVE77</th>
<th>PROVIDER PERSPECTIVE77</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Equally prevalent in men and women75</td>
<td>• First-generation antipsychotics</td>
<td>• Paliperidone is a centrally active dopamine type 2 receptor antagonist and serotonin type 2 receptor antagonist50</td>
<td>• Autonomy</td>
<td>• Benefits to adherence78</td>
</tr>
<tr>
<td>• 1.1% prevalence in U.S.49</td>
<td>• Second-generation antipsychotics</td>
<td>• Only FDA-approved LAI for schizoaffective disorder79</td>
<td>• Convenience of treatment</td>
<td>• Fear of coercion</td>
</tr>
<tr>
<td></td>
<td>• Clozapine</td>
<td></td>
<td>• Fear of injections</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Combination therapy</td>
<td></td>
<td>• Lack of understanding about disease or therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• LAI antipsychotic agents</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table H2. Prior evidence and RWE for including new evidence in the clinical studies section of the label for Invega Sustenna®

<table>
<thead>
<tr>
<th>PRIOR EVIDENCE</th>
<th>RWE⁴⁹,⁵⁰</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Three short-term (13-week) RCTs (schizophrenia)</td>
<td>• PRIDE</td>
</tr>
<tr>
<td>– Study design: randomized double-blind placebo-controlled fixed-dose trial</td>
<td>– Study design: randomized prospective open-label event-monitoring board-blinded parallel-group study</td>
</tr>
<tr>
<td>– Population: acutely relapsed adult inpatients who meet DSM-IV criteria for schizophrenia</td>
<td>Screening phase of ≤2 weeks</td>
</tr>
<tr>
<td>– Primary outcome: change of positive and negative symptoms of schizophrenia and general psychopathology measured by the Positive and Negative Syndrome Scale (PANSS)</td>
<td>15-month randomized open-label treatment phase</td>
</tr>
<tr>
<td>– Intervention</td>
<td>– Population: adults aged 18–65 with DSM-IV schizophrenia, confirmed by Mini-International Neuropsychiatric Interview version 6</td>
</tr>
<tr>
<td>PSY-3007: comparing initial deltoid injection of 234 mg and 3 fixed doses (39 mg/4 wk, 156 mg/4 wk, 234 mg/4 wk) of Invega Sustenna® to placebo</td>
<td>Taken into custody ≥2 times within 2 years</td>
</tr>
<tr>
<td>PSY-3003: comparing 3 fixed doses (78 mg/4 wk, 156 mg/4 wk, 234 mg/4 wk) of Invega Sustenna® to placebo</td>
<td>≥1 incarceration within 2 years</td>
</tr>
<tr>
<td>PSY-3004: comparing 3 fixed doses (39 mg/4 wk, 78 mg/4 wk, 156 mg/4 wk) of Invega Sustenna® to placebo</td>
<td>Release from custody within 90 days of screening</td>
</tr>
<tr>
<td>• SCH-201</td>
<td>– Intervention: comparing Invega Sustenna® (paliperidone palmitate) with oral antipsychotics (aripiprazole, haloperidol, olanzapine, paliperidone, perphenazine, quetiapine, and risperidone)</td>
</tr>
<tr>
<td>– Study design: short-term (9-week) double-blind randomized placebo-controlled fixed-dose trial</td>
<td>– Primary outcome: time to treatment failure</td>
</tr>
<tr>
<td>– Population: acutely relapsed adult inpatients who meet DSM-IV criteria for schizophrenia</td>
<td>Clinical pharmacology studies</td>
</tr>
<tr>
<td>– Intervention: comparing 2 fixed doses (78 mg/4 wk and 156 mg/4 wk) of Invega Sustenna® to placebo</td>
<td>Non-clinical toxicology studies</td>
</tr>
<tr>
<td>– Primary outcome: change of positive and negative symptoms of schizophrenia and general psychopathology measured by PANSS</td>
<td>– Population: adults who met DSM-IV criteria for schizophrenia</td>
</tr>
<tr>
<td>• PSY-3001</td>
<td>– Intervention: randomized to same dose of Invega Sustenna® as stabilization phase (39 mg/4 wk, 78 mg/4 wk, 156 mg/4 wk) or placebo until relapse</td>
</tr>
<tr>
<td>– Study design: long-term double-blind placebo-controlled flexible-dose study</td>
<td>– Primary outcome: time to relapse</td>
</tr>
<tr>
<td>– Population: adults who met DSM-IV criteria for schizophrenia</td>
<td>Screening phase of ≤2 weeks</td>
</tr>
<tr>
<td>– Intervention: randomized to same dose of Invega Sustenna® as stabilization phase (39 mg/4 wk, 78 mg/4 wk, 156 mg/4 wk) or placebo until relapse</td>
<td>15-month randomized open-label treatment phase</td>
</tr>
<tr>
<td>– Primary outcome: time to relapse</td>
<td>– Population: adults who met DSM-IV criteria for schizoaffective disorder, confirmed by structured clinical interview for DSM-IV disorders</td>
</tr>
<tr>
<td>• SCA-3004</td>
<td>– Intervention: comparing Invega Sustenna® (78 mg, 117 mg, 156 mg, 234 mg) to placebo</td>
</tr>
<tr>
<td>– Study design: long-term double-blind placebo-controlled flexible-dose randomized-withdrawal trial</td>
<td>– Primary outcome: time to relapse</td>
</tr>
<tr>
<td>– Population: adults who met DSM-IV criteria for schizoaffective disorder, confirmed by structured clinical interview for DSM-IV disorders</td>
<td>Clinical pharmacology studies</td>
</tr>
<tr>
<td>– Intervention: comparing Invega Sustenna® (78 mg, 117 mg, 156 mg, 234 mg) to placebo</td>
<td>Non-clinical toxicology studies</td>
</tr>
<tr>
<td>– Primary outcome: time to relapse</td>
<td>Non-clinical toxicology studies</td>
</tr>
</tbody>
</table>
APPENDIX I. HYPOTHETICAL CASE STUDY: BIOLOGIC APPROVED FOR CROHN'S DISEASE

DISCLAIMER: This hypothetical case study is not intended to be used as a regulatory or evidence-generation strategy to support effectiveness claims. Rather, the intent is to foster a discussion on the potential of RWE. To evaluate the ability of RWE to contribute to the evidence package, as evaluated through a totality of evidence approach, some questions have been developed for readers’ consideration.

**Questions for Consideration**

1. Can RWE be used to adequately answer the research question informing the labeling change?
   a. If yes, why?
   b. If not, why not?
2. Under what conditions, if any, might an RCT be required as part of a new evidence package for these case studies?
3. What additional studies may strengthen the new evidence package?

**Regulatory Context**

Consider a hypothetical biologic (IBDBIO2) currently approved for inducing and maintaining remission in adult patients with moderately to severely active Crohn's disease (CD). The sponsor is seeking a labeling change to add a new indication, inducing and maintaining remission in adult patients with moderately to severely active ulcerative colitis (UC).

**Clinical Context**

*Disease Background*

UC and CD are both autoimmune diseases and types of inflammatory bowel disease that significantly impact quality of life. UC affects only the large intestine, or colon, whereas CD affects any part of the gastrointestinal tract. UC manifests in recurring colon mucosal layer inflammation. CD and UC affect men and women equally (Table 1). The prevalence of UC and CD is varied; however, one estimate indicates that UC and CD prevalence increased between 2000 and 2011 from 214 to 286 cases per 100,000 persons for UC and from 174 to 247 cases per 100,000 persons for CD.

CD and UC share similar symptoms, with about 10% to 15% overlap. While typical phenotypes differ for UC and CD, most biologics are effective in treating both diseases. Additionally, C-reactive protein (CRP) levels correlate with response in UC and CD patients, although no gold-standard biomarker exists. Additional clinical context information can be found in Table 1.
Current Therapies and Level of Unmet Need

Tumor necrosis factor (TNF) inhibitors, or anti-TNFs, are a typical monoclonal antibody (MAB) treatment option for patients with moderately to severely active UC. However, patients can suffer from primary non-response (PNR), in which the patient never responds to treatment after induction. The incidence of PNR ranges from 10%–30%. Patients can also suffer from secondary loss of response (LOR), in which the patient responds to treatment after induction but stops responding to treatment at a later time. The incidence of LOR is difficult to determine, as it varies depending on whether it is measured in terms of dose intensification or drug discontinuation. PNR and LOR are managed by intensifying the dose, adding immunomodulators, or switching to a therapy in a different class. If patients repeatedly suffer from PNR or LOR, the existing therapies can be exhausted. Surgical bowel removal is the last resort. Anti-TNFs can also be associated with a small increased risk of lymphoma, especially when the biologic is combined with another immunosuppressant.

Other MABs indicated to treat moderately to severely active UC include anti-α4 integrin antibodies, such as vedolizumab, and anti-interleukin 12/23 antibodies, such as ustekinumab. For some anti-α4 integrins, there is an increased risk of developing progressive multifocal leukoencephalopathy (PML), a severe neurological condition that can occur during severe immunosuppression. Vedolizumab may be beneficial for patients with weakened immune systems as it does not typically lead to increased infection or malignancy. Ustekinumab may be beneficial for patients who have experienced PNR or LOR to anti-TNFs or as a first-line biologic due to failure to respond to other therapies.

Proposed Therapy

IBDBIO2 is a MAB with a different mechanism of action than the biologics used to treat UC currently on the market. Unlike some other biologics approved for treatment of CD and UC, IBDBIO2 does not increase the risk of developing PML.

Patient and Provider Perspectives

UC patients have reported a desire for treatments that allow them to perform daily activities and manage their pain. However, patients and providers have varying treatment goals. For example, a treatment goal for a physician may be reduction in inflammation, whereas a patient’s treatment goal may be more focused on quality of life (such as less time spent in the bathroom per day). Additionally, patients have reported concerns that providers do not recognize the effect of UC on mental health. Physicians consider biologics as a last resort pharmaceutical treatment for UC due to fear of side effects, such as increased risk of infection and malignancies, but may prescribe a biologic if it is believed to significantly improve quality of life and lead to remission. Patients also might believe that biologics should be reserved for a higher severity form of UC than their current stage.
Evidence

Prior Evidence

Prior evidence consisted of clinical pharmacology, non-clinical toxicology studies, and phase II/phase III clinical trial data for CD, where the co-primary outcomes, remission and mucosal healing, were measured using the Crohn’s Disease Activity Index (CDAI) scores and the Crohn’s Disease Endoscopic Index of Severity (CDEIS) scale, respectively. Additional information about the studies can be found in Table I2.

New Evidence: Strengths and Limitations

New evidence consisting of pharmacokinetic (PK) data suggests consistency between CD and UC, motivating the exploration of IBDBIO2 for UC. First, a patient registry established from a network of practices with UC patients was created to support secondary use of the data for research purposes. EHR linkage and electronic case report forms, in addition to some patient surveys, were also available. UC diagnosis was determined in part through the Partial Mayo Score, which is used in both clinical trials and clinical practice to assess disease activity and severity. The Partial Mayo Score was collected fairly regularly, though some data were missing and time points varied due to real-world appointments. Endoscopy data were present, but limited, as is typical in clinical practice. The analysis showed that most UC patients who experienced PNR and LOR with previous treatments had positive response when using IBDBIO2. Outcomes were not available for all patients, but sensitivity analyses suggest consistent evidence for effectiveness: response and remission rates (including steroid-free remission) were comparable to pivotal trials of approved UC therapies. IBDBIO2 showed an acceptable safety profile that was comparable to pivotal UC trials and existing UC RWE studies.

Subsequently, an adequately powered, prespecified large-scale pragmatic trial was also conducted in UC patients, where patients were randomized to either IBDBIO2 or a standard of care treatment for UC to measure the comparative effectiveness of IBDBIO2. The primary outcome included colectomy surgery in the inpatient setting. The pragmatic trial showed significant benefit in tolerability of treatment and consistent effectiveness compared to standard of care therapies. Additional information about the studies can be found in Table I2.

Regulatory Decision

In determining whether IBDBIO2 should receive a labeling change to include UC patients, the regulatory decision would likely rely highly on the disease biology and clinical context, because effective alternative treatments are more limited. Due to heterogeneity in the UC population, the consistency in effectiveness and the safety profile in UC patients would also be an important consideration.

* To calculate CDAI scores, physicians collect information directly from patients on 8 items: patient-reported stool pattern, antidiarrheal use, average abdominal pain over 7 days, general well-being over 7 days, complications, finding of an abdominal mass, anemia, and weight change. Physicians then multiply each item by the weighting score. CDAI scores are used to determine the severity of CD activity, with scores of 150 or below suggesting remission.

† The Partial Mayo Score includes all points of the Mayo Score, with the exception of mucosal appearance at endoscopy. The Partial Mayo Score evaluates stool frequency (normal, 1–2 stools/day more than normal, 3–4 stools/day more than normal, or >4 stools/day more than normal); rectal bleeding (none, visible blood with stool less than half of the time, visible blood with stool half of the time or more, or passing blood alone); and physician rating of disease activity (normal, mild, moderate, or severe).
### Table 11. Clinical context for IBDBIO2 labeling change to include patients with UC

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>TREATMENT ALTERNATIVES</th>
<th>THERAPY</th>
<th>PATIENT PERSPECTIVE</th>
<th>PROVIDER PERSPECTIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>• UC is a chronic disease, with heavy quality-of-life impact</td>
<td></td>
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<tr>
<td>• Characterized by recurring episodes of inflammation limited to the mucosal layer of the colon</td>
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<tr>
<td>• Most biologics effective at treating both diseases</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Many biologic therapies exist for UC, but patients can have either PNR or LOR and potential exhaustion of existing therapeutics</td>
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</tr>
<tr>
<td>• A significant number of patients do not respond to existing therapies</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>• Surgical bowel removal is last resort</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Current MABs include anti-TNFs (infliximab, adalimumab, certolizumab, and golimumab), anti-α4 integrins (vedolizumab and natalizumab), and anti-interleukin 12/23 antibodies (ustekinumab)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• MAB with a mechanism of action different from other biologics used to treat IBD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• No PML warning</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Tolerance of therapy versus symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Unmet need for patients who exhaust prior treatment options</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Ability to do daily activities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Pain management</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Perception of disease severity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Quality of life</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Variation in treatment goals</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Biologics considered last resort pharmaceutical treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Quality of life</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Lack of efficacy with current treatments</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

### Table 12. Prior evidence and RWE for IBDBIO2 labeling change to include patients with UC

<table>
<thead>
<tr>
<th>PRIOR EVIDENCE</th>
<th>RWE</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Clinical trial 1 (phase II)</td>
<td></td>
</tr>
<tr>
<td>• Study design: randomized double-blinded placebo-controlled fixed-dose trial</td>
<td></td>
</tr>
<tr>
<td>• Population: adults with Crohn’s disease</td>
<td></td>
</tr>
<tr>
<td>• Intervention: comparing 3 fixed doses of a drug to placebo to assess efficacy</td>
<td></td>
</tr>
<tr>
<td>• Primary outcomes: mucosal healing (measured by CDEIS scale) and remission (measured by CDAI scores)</td>
<td></td>
</tr>
<tr>
<td>• Clinical trial 2 (phase III)</td>
<td></td>
</tr>
<tr>
<td>• Study design: randomized double-blinded placebo-controlled fixed-dose trial</td>
<td></td>
</tr>
<tr>
<td>• Population: adults with Crohn’s disease</td>
<td></td>
</tr>
<tr>
<td>• Intervention: comparing drug to placebo to assess efficacy</td>
<td></td>
</tr>
<tr>
<td>• Primary outcomes: mucosal healing (measured by CDEIS scale) and remission (measured by CDAI scores)</td>
<td></td>
</tr>
<tr>
<td>• Clinical pharmacology studies</td>
<td></td>
</tr>
<tr>
<td>• Non-clinical toxicology studies</td>
<td></td>
</tr>
<tr>
<td>• Pragmatic trial</td>
<td></td>
</tr>
<tr>
<td>• Study design: randomized open-label parallel-group trial for one year of follow up</td>
<td></td>
</tr>
<tr>
<td>• Population: adults with UC</td>
<td></td>
</tr>
<tr>
<td>• Intervention: comparing IBDBIO2 with standard of care treatments for UC (infliximab, adalimumab, golimumab, vedolizumab)</td>
<td></td>
</tr>
<tr>
<td>• Primary outcome: colectomy surgery due to treatment failure</td>
<td></td>
</tr>
<tr>
<td>• EHR-linked UC patient registry</td>
<td></td>
</tr>
<tr>
<td>• Partial Mayo Score data and some endoscopy data were available</td>
<td></td>
</tr>
<tr>
<td>• Response and remission rates were comparable to pivotal RCTs</td>
<td></td>
</tr>
<tr>
<td>• Patients who previously failed treatments had positive response</td>
<td></td>
</tr>
<tr>
<td>• PK data available suggest consistency between CD and UC</td>
<td></td>
</tr>
<tr>
<td>• Animal studies show UC effectiveness, including mucosal healing</td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX J. HYPOTHETICAL CASE STUDY: LONG-ACTING BRONCHODILATOR APPROVED FOR COPD

DISCLAIMER: This hypothetical case study is not intended to be used as a regulatory or evidence-generation strategy to support effectiveness claims. Rather, the intent is to foster a discussion on the potential of RWE. To evaluate the ability for RWE to contribute to the evidence package, as evaluated through a totality of evidence approach, some questions have been developed for readers’ consideration.

Questions for Consideration

1. Can RWE be used to adequately answer the research question informing the labeling change?
   a. If yes, why?
   b. If not, why not?
2. Under what conditions, if any, might an RCT be required as part of a new evidence package for these case studies?
3. What additional studies may strengthen the new evidence package?

Regulatory Context

Consider LAMCO, a hypothetical long-acting bronchodilator currently indicated for treating airflow obstruction as measured through FEV$_1$* in patients with chronic obstructive pulmonary disease (COPD) seeking to add a new indication for reducing COPD exacerbations. Exacerbations are defined as two or more respiratory symptoms (cough, sputum, wheezing, dyspnea, or chest tightness) that result in a treatment change. A change in treatment can include any or all of the following: antibiotics, systemic corticosteroids, or hospitalization.

Clinical Context

Disease Background

COPD is a progressive pulmonary disease in which a patient has increased trouble breathing over time due to airflow limitations. COPD is often due to substances that cause lung irritation over time, such as cigarette smoke or air pollution, and affects about 15.7 million Americans. COPD is associated with high morbidity and mortality and is the fourth leading cause of death in the United States. In 2010, there were 32.2 estimated hospitalizations for COPD per 10,000 patients and 72 ER visits for COPD per 10,000 patients. Additional clinical context information can be found in Table J1.

Current Therapies and Level of Unmet Need

COPD can be treated with long-acting bronchodilators, such as long-acting muscarinic agonist (LAMAs) including aclidinium, glycopyrronium bromide, umeclidinium, and tiotropium. Aclidinium, glycopyrronium bromide, and umeclidinium are indicated for maintenance treatment of airflow

* Forced expiratory volume (FEV$_1$) is the amount of air a person can exhale in a forced breath in one second. COPD is typically diagnosed when a patient has a FEV$_1$/FVC ratio of less than 70%, where FVC is forced vital capacity.
obstruction in patients with COPD. Tiotropium is indicated for maintenance treatment of bronchospasm in COPD patients as well as for reducing COPD exacerbations. For tiotropium, reduction of exacerbations was evaluated by two double-blind RCTs.\textsuperscript{97} LAMAs are associated with improved symptoms and health status and can improve pulmonary rehabilitation effectiveness.\textsuperscript{96} While other treatment alternatives exist for COPD, LAMAs were shown in clinical trials to cause a greater decrease in exacerbations as compared to long-acting $\beta_2$-agonists (LABAs).\textsuperscript{96}

**Proposed Therapy**

LAMCO is a LAMA currently indicated for treatment of airflow obstruction in COPD patients.

**Patient and Provider Perspectives**

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) standards recommend using: 1) FEV$_1$ to assess disease severity, 2) Modified British Medical Research Council (mMRC)\textsuperscript{*} or COPD Assessment test (CAT)\textsuperscript{†} to assess symptoms, and 3) history of exacerbations to categorize patients for treatment.\textsuperscript{96} However, reduction in FEV$_1$ is not strongly correlated with changes in health status, breathlessness, or patient quality-of-life outcomes.\textsuperscript{98} In a cross-sectional study, patients reported a change in breathlessness that was associated with only a 4% difference in FEV$_1$.\textsuperscript{99} The change in baseline FEV$_1$ also cannot capture other important information that contributes to health status, such as ability to conduct functional activities.\textsuperscript{98} FEV$_1$ measurements may also underestimate COPD presence in younger patients and overestimate in older patients, as decreased airflow may occur due to natural aging.\textsuperscript{100}

Measures of FEV$_1$ are intangible to patients, who have expressed a desire to understand not the measure of lung function, but rather how their lung impairment affects their quality of life as well as how they feel and function. Patients mainly desire to reduce symptoms and exacerbations, which may improve quality of life. Adding a patient-centered outcome, such as reduction of symptoms of an exacerbation, to the label can help patients quantify their disease burden.

Physicians also consider quality of life and symptom control as well as prevention of disease progression in treating COPD.\textsuperscript{101} A provider might be more likely to prescribe a drug that leads to fewer exacerbations, if it increases quality of life for patients and decreases medical costs.

**Evidence**

**Prior Evidence**

Prior evidence includes phase II and phase III trial data for treatment of COPD with a long-acting bronchodilator where FEV$_1$ is the primary outcome. Additional information about the studies can be found in Table J2.

\* mMRC is a scale that assigns a grade from 0 to 4 based on symptoms of dyspnea.

\† CAT is an 8-question assessment to evaluate patient symptoms. Each item on the assessment is scored between 0 and 5, where patients are provided interpretations of a "0" score and a "5" score for each item. For example, in regard to patient energy level, patients can rate from 0 to 5, where 0 indicates "I have lots of energy" and 5 indicates "I have no energy at all."
New Evidence: Strengths and Limitations

New evidence includes an analysis of a large claims database and an analysis of a large EHR database, both of which were prespecified and adequately powered. The primary outcomes were the proportion of patients with symptoms of COPD exacerbations and the proportion of patients with hospitalization due to COPD exacerbations. In the claims data, a validated algorithm was used to identify patients with COPD exacerbations and hospitalizations related to COPD exacerbations. Hospitalizations and symptoms of COPD exacerbations were extracted from the EHR data. Both studies demonstrated that the proportion of COPD exacerbations among patients taking LAMCO was significantly less than the proportion of COPD exacerbations in patients taking a standard of care LAMA. Additional information about the studies can be found in Table J2.

Regulatory Decision

The regulatory decision will likely largely rely on prior evidence for the previously approved LAMAs and the safety and efficacy of LAMCO. The use of RWE studies to support a labeling change for LAMCO highlights the importance of RWD to support the patient perspective by seeking to add a patient-centered endpoint to the label. LAMCO differentiates itself from other LAMAs with an indication for reduced exacerbations as it is the first to demonstrate exacerbation reduction in clinical care settings.

Table J1. Clinical context for LAMCO labeling change to add a new indication for reducing COPD exacerbations

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>TREATMENT ALTERNATIVES96</th>
<th>THERAPY</th>
<th>PATIENT PERSPECTIVE</th>
<th>PROVIDER PERSPECTIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Characterized by airflow limitation92</td>
<td>LAMAs include tiotropium, aclidinium, glycopyrronium bromide, and umeclidinium</td>
<td>LAMA</td>
<td>• Reduction in FEV₁ is hard to understand and needs a more patient-friendly outcome</td>
<td>• Focus on disease progression</td>
</tr>
<tr>
<td>• Affects approximately 15.7 million Americans94</td>
<td></td>
<td></td>
<td>• Quality of life</td>
<td>• Decreased cost with decreased ER visits</td>
</tr>
<tr>
<td>• Associated with high morbidity and mortality95</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Table J2. Prior evidence and RWE for LAMCO labeling change to add a new indication for reducing COPD exacerbations

<table>
<thead>
<tr>
<th>PRIOR EVIDENCE</th>
<th>RWE</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Clinical trial 1 (phase II)</td>
<td>• Analysis of a large claims database comparing LAMCO to a standard of care LAMA</td>
</tr>
<tr>
<td>− Study design: randomized double-blind placebo-controlled fixed-dose trial</td>
<td>• Analysis of a large EHR database comparing LAMCO to a standard of care LAMA</td>
</tr>
<tr>
<td>− Population: adults with COPD</td>
<td>• Co-primary outcomes for both analyses: proportion of patients with COPD exacerbations and the proportion of patients with hospitalizations due to COPD exacerbations</td>
</tr>
<tr>
<td>− Intervention: comparing drug to placebo to assess efficacy</td>
<td></td>
</tr>
<tr>
<td>− Primary outcome: FEV₁</td>
<td></td>
</tr>
<tr>
<td>• Clinical trial 2 (phase III)</td>
<td></td>
</tr>
<tr>
<td>− Study design: randomized double-blind placebo-controlled fixed-dose trial</td>
<td></td>
</tr>
<tr>
<td>− Population: adults with COPD</td>
<td></td>
</tr>
<tr>
<td>− Intervention: comparing drug to placebo to assess efficacy</td>
<td></td>
</tr>
<tr>
<td>− Primary outcome: FEV₁</td>
<td></td>
</tr>
<tr>
<td>• Clinical pharmacology studies</td>
<td></td>
</tr>
<tr>
<td>• Non-clinical toxicology studies</td>
<td></td>
</tr>
</tbody>
</table>


56. U.S. Food and Drug Administration. Center for Drug Evaluation and Research Application Number: 761036orig1s000. Pharmacology Review(s); 2015.


63. U.S. Food and Drug Administration. Center for Drug Evaluation and Research. Application Number: 205755orig1s000. Other Review(s); 2014.


