Introduction

Breakthrough Therapy Designation (BTD), established by the Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012, is one of several programs available to the U.S. Food and Drug Administration (FDA) to expedite the development and review of drugs and biologics for serious diseases and conditions. In order to qualify for a breakthrough therapy designation, a candidate therapy must be intended to treat a serious or life-threatening illness, and preliminary clinical evidence must indicate that the therapy may demonstrate a substantial improvement over existing therapies on at least one clinically significant endpoint. FDA released draft guidance to industry on the breakthrough therapy designation program in June 2013 and final guidance in May 2014.

In cooperation with key partners from industry, academia, and patient and disease advocacy groups, the Center for Health Policy at the Brookings Institution is convening a public meeting that will seek to enhance clarity and understanding of the qualifying criteria for BTD, using case studies drawn from the last two and a half years of program implementation. This workshop is being convened under a cooperative agreement between FDA and the Brookings Institution.

Developing the Breakthrough Therapy Designation Program

FDA currently maintains four expedited programs: breakthrough therapy designation, fast track designation, priority review, and accelerated approval (see Table 1 for a summary of these programs). All of these programs are intended to facilitate and expedite development and review of drugs that address unmet medical need in the treatment of serious or life-threatening conditions. Accelerated approval (which was established under Subpart H of FDA’s New Drug, Antibiotic, and Biological Products regulations) and priority review (which was created through the passage of the Prescription Drug User Fee Act) were developed in 1992. Fast track designation was established in 1997 under section 112 of the Food and Drug Administration Modernization Act. These mechanisms have all played a meaningful role in reducing development and review timelines for the drugs that meet their criteria.

In recent years, advances in the science of drug discovery and development—particularly for targeted therapies in the field of oncology—have begun producing drugs that show extraordinary effects at increasingly early stages of testing. These advances have raised important questions about the traditional approach to clinical development, and have led some to call for a new expedited development and review process that would be specifically applied to therapies that showed early promise of significant clinical benefit. FDA acknowledged these issues in a 2011 report on driving biomedical innovation, and pledged to hold a series of scientific meetings to explore feasible approaches to developing a new expedited development pathway.

In pursuit of this goal, Friends of Cancer Research and the Brookings Institution convened a multi-stakeholder panel at the 2011 Conference on Clinical Cancer Research entitled, “Development Paths for New Drugs with Large Effects Seen Early.” The resulting white paper helped to inform the drafting of Section 902 of FDASIA, which provides the statutory framework for BTD.
Table 1: Overview of FDA’s Expedited Development and Review Programs

<table>
<thead>
<tr>
<th>Qualifying Criteria</th>
<th>Fast Track Designation</th>
<th>Breakthrough Therapy Designation</th>
<th>Accelerated Approval</th>
<th>Priority Review Designation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qualifying Criteria</td>
<td>• A drug that is intended to treat a serious condition, AND • Clinical or nonclinical data demonstrate potential to address an unmet medical need</td>
<td>• A drug that is intended to treat a serious condition, AND • Preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapies on a clinically significant endpoint(s)</td>
<td>• A drug that treats a serious condition, AND • Generally provides meaningful advantage over available therapies, AND • Demonstrates an effect on a surrogate endpoint that is reasonably likely to predict patient benefit</td>
<td>• An application (original or efficacy supplement) for a drug that treats a serious condition, AND • If approved, would provide a significant improvement in safety and/or effectiveness</td>
</tr>
<tr>
<td>Timeline for FDA Response</td>
<td>• Within 60 days of request receipt</td>
<td>• Within 60 days of request receipt</td>
<td>• No specified timeline.</td>
<td>• Within 60 days of receipt of original BLA, NDA or efficacy supplement</td>
</tr>
<tr>
<td>Program Features</td>
<td>• Actions to expedite development and review, such as opportunities for frequent interactions with the review team • Rolling Review</td>
<td>• Intensive guidance on efficient drug development • Organizational commitment from FDA, involving senior managers • Rolling Review • Other actions to expedite review</td>
<td>• Approval based on an effect on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict a drugs’ clinical benefit • Drug sponsor must conduct post-approval studies to confirm clinical benefit</td>
<td>• Reduces FDA review period from 10 months to 6</td>
</tr>
</tbody>
</table>

Adapted from FDA’s Guidance for Industry: Expedited Programs for Serious Conditions - Drugs and Biologics

Defining Breakthrough Therapy Designation

Breakthrough therapy is distinct from FDA’s other expedited programs both in terms of the level of evidence required and the type of engagement that sponsors subsequently receive from the FDA during clinical development. As noted above, in order to qualify as a breakthrough therapy there must be preliminary clinical evidence that indicates a therapy may demonstrate substantial improvement over available therapies on at least one clinically significant endpoint. Fast track, by contrast, may be granted based on either clinical or nonclinical data, and these data need only demonstrate that the therapy has the potential to address an unmet medical need.
Once a breakthrough therapy designation is granted, FDA commits to providing the sponsor with timely advice and interactive communications throughout the development process. These interactions can include the use of interim analyses of trial data as well as proposals for alternative clinical trial designs that may lead to smaller or more efficient trials. As part of the process, FDA appoints a cross-disciplinary project lead that serves as a scientific liaison between members of the review team, facilitating the coordination of internal interactions as well as communication with the sponsor through the review division’s regulatory health project manager. Where appropriate, FDA will involve senior agency staff from various disciplines. Drugs and biologics that receive the breakthrough therapy designation are also eligible to request rolling review of the drug application. As with fast track designation, FDA reserves the right to rescind the designation if subsequent evidence demonstrates that the therapy no longer meets the criteria or the program is no longer being pursued. Breakthrough therapy designation can also be used in combination with the Agency’s other expedited programs to further expedite the drug’s time to market. For example, a drug can have a breakthrough therapy designation and also receive approval under the accelerated approval program or through priority review. Of the ten drugs that were designated as breakthrough therapies and subsequently approved by FDA in 2014, all had received at least two other expedited program designations (seven fast track, ten priority review, and five accelerated approval).

Applying the Breakthrough Therapy Designation Criteria in Practice
In considering a request for BTD, FDA relies on three primary considerations: 1) the quantity and quality of the clinical evidence being submitted in a designation request; 2) the available therapies that the drug is being compared to; and 3) the magnitude of treatment effect shown. Although these considerations are clear, it is difficult to define a single threshold that a therapy must meet in order to receive the designation. Requests for breakthrough therapy designation cover a wide range of therapeutic areas, and although the Expedited Programs guidance recommends that requests be submitted no later than end-of-phase 2, requests may be submitted at different stages of drug development with quite different levels of supporting evidence. Requests can also differ significantly in terms of the amount of clinical trial data included (i.e., differences in sample size, phase of drug development), trial design (i.e., choice of endpoints, single-arm versus, randomized controlled), and trial results (i.e., the magnitude of treatment effect size seen.)

As of March 2015, FDA has received a total of 293 requests for breakthrough therapy designation. Of these, the Agency granted a total of 82—less than 1 in 3. Of the 244 requests submitted to the Center for Drug Evaluation and Research (CDER), 71 (or 30%) were granted. Of the 49 requests submitted to the Center for Biologics Evaluation and Research (CBER), 11 (or 22%) were granted. In contrast, between 1998 and 2007 CDER received 566 fast track designation requests, and granted 424 (75%), while CBER received 311 fast track designation requests, and granted 194 (62%). The two designations have different criteria—the “bar” for granting a BTD request is higher, for example—but the higher rate of success for fast track designation requests suggests that sponsors may have relatively less clarity on what qualifies as a breakthrough therapy as compared to what qualifies for fast track. In order to shed more light on this issue—as well as improve the success rate of future applications—the agency is currently conducting an in-house analysis of breakthrough therapy designation requests and the FDA review of these requests. CDER will present a summary of the full analysis at today’s workshop.
Meeting Goals

Today’s workshop will serve to advance the discussion of the qualifying criteria for BTD, as well as clarify the Agency’s application of the qualifying criteria to varying clinical development programs. Using actual and hypothetical case studies from diverse clinical areas—including oncology, neurology, psychiatry, infectious disease, and hematology—the discussion will highlight the major industry considerations in deciding to submit a request for breakthrough therapy designation, explore the agency’s application of the qualifying criteria for each candidate, and discuss what factors led to the request being granted or denied. (See the Appendix for a more detailed presentation of each case study.) The discussion will also focus on key strategies for ensuring that the qualifying criteria are understood by all stakeholders.

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7 Food and Drug Administration Safety and Innovation Act, S.3187, § 902 (2012)


9 U.S. Food and Drug Administration website “CBER Approvals For Breakthrough Therapy Designated Drugs” accessed on April 17, 2015.


Appendix: Breakthrough Therapy Designation Case Studies
Breakthrough Therapy Designation: Exploring the Qualifying Criteria, Session II
Case Study 1: Keytruda

Breakthrough Therapy Designation Request Basics

<table>
<thead>
<tr>
<th>Sponsor:</th>
<th>Merck Sharp and Dohme Corporation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug:</td>
<td>Keytruda (pembrolizumab, MK-375)</td>
</tr>
</tbody>
</table>
| Indication:        | (1) Treatment of unresectable or metastatic melanoma that is refractory to ipilimumab treatment  
|                    | (2) Treatment of unresectable or metastatic melanoma in patients who have not received prior ipilimumab therapy |
| Division/Therapeutic Area: | Office of Hematology and Oncology Products, Division of Oncology Products 2, CDER, FDA |
| Date BTDR submitted: | November 21, 2012 |
| Date of BTDR grant:  | January 17, 2013 |

Overview

Disease and intended population
Melanoma is a serious and life-threatening condition. It is the fifth most common cancer in men and seventh in women in the United States. The five year survival rate is 15% for patients who present with unresectable or metastatic disease. In 2014, it is estimated that there were 76,100 new melanoma cases and 9,710 deaths from melanoma in the U.S. (American Cancer Society: Cancer Facts and Figures 2014). According to Surveillance, Epidemiology and End Results (SEER) data, between 2004 and 2010, approximately 84% of patients were diagnosed with localized disease, 9% with regional disease, and 4% with distant metastatic disease. While patients with localized disease have an excellent long-term prognosis, patients who are diagnosed with or develop metastatic disease have a median overall survival of less than one year and represent a patient population with an unmet medical need (Howlader N, et. al. 2014).

Drug description and relevant regulatory history
Pembrolizumab is a human monoclonal IgG4 antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. The blockade enhances functional activity of lymphocytes, which is postulated to facilitate tumor regression through immune rejection. The PD-1 pathway is a major immune control switch that may be engaged by ligands expression in the tumor microenvironment to overcome active anti-tumor specific T-cell immune surveillance. The high expression of PD-L1 (ligand for PD-1) on some tumor cells has been found to correlate with poor prognosis and survival in various cancers. Merck Sharp and Dohme (Merck) states that the observed correlation of clinical prognosis with PD-L1 expression in multiple cancers suggests a critical role in tumor evasion for the PD-1/PD-L1 pathway.

Summary of Clinical Evidence Submitted with the BTDR

Available therapies
Prior to 2011, no drug was shown to improve survival in patients with metastatic melanoma. However, since 2011, FDA has approved two drugs for the treatment of metastatic melanoma based on demonstration of improved overall survival: ipilimumab and vemurafenib. Ipilimumab, a recombinant human IgG1 immunoglobulin monoclonal antibody which binds to the cytotoxic T-lymphocyte associated antigen 4 (CTLA-4), a negative regulator of T-cell activation, demonstrated a 4 month
improvement in median overall survival compared to a gp100 peptide tumor vaccine. Vemurafenib, a small molecule inhibitor of the BRAF serine-threonine kinase, demonstrated an improvement in overall survival compared to dacarbazine [HR 0.44; 95% CI (0.33, 0.59); median OS not reached on vemurafenib arm, median OS 7.9 months on dacarbazine arm]. Of note, use of vemurafenib is limited to patients with BRAF V600E mutation-positive melanoma as detected by an FDA approved test (cobas® 4800 BRAF V600 Mutation Test), a subset consisting of approximately 50% of patients with advanced melanoma.

Also of note, the approved indications for ipilimumab and vemurafenib do not limit use of either product to a specific line of therapy in the treatment of patients with unresectable or metastatic melanoma. Other FDA-approved drugs for the treatment of patients with metastatic or unresectable melanoma are dacarbazine and interleukin-2; neither of these two drugs has demonstrated an improvement in overall survival.

Table 1 is a list of FDA-approved therapies for metastatic melanoma with details on clinical efficacy outcomes for each drug:

**Table 1. FDA-approved drugs for Metastatic Melanoma at the Time of the Breakthrough Request**

<table>
<thead>
<tr>
<th>Druga</th>
<th>Approval</th>
<th>Trial Design</th>
<th>Endpoint(s)</th>
<th>Clinical Benefit/Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTIC (dacarbazine)b</td>
<td>1975</td>
<td>Single arm trials</td>
<td>ORR</td>
<td>ORR 10-20%</td>
</tr>
<tr>
<td>Proleukinb (interleukin-2)</td>
<td>1998</td>
<td>Single-arm, multicenter trial</td>
<td>ORR</td>
<td>ORR 16% (CR 6%); DOR 9 months (1-122+)</td>
</tr>
<tr>
<td>Yervoyb (ipilimumab)</td>
<td>2011</td>
<td>Randomized, open-label, active-controlled, 3-arm trial</td>
<td>OS, ORR</td>
<td>Ipilimumab alone: mOS: 10 months HR 0.66 (0.51, 0.87) Best ORR: ipi + gp100: 10.9% ipi: 10.9% gp100: 1.5% DOR: ipi+gp100: 11.5 months ipi: not reached gp100: not reached</td>
</tr>
<tr>
<td>Zelborafc (vemurafenib)</td>
<td>2011</td>
<td>Randomized, active-controlled</td>
<td>OS, PFS, ORR</td>
<td>mOS: not reached HR: 0.44 (0.33, 0.59) mPFS: 5.3 months HR: 0.26 (0.20, 0.33) Best ORR: Vemurafenib: 48.4% CR 0.9% PR 47.4% DTIC†: 5.5% PR: 5.5%</td>
</tr>
</tbody>
</table>

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*a Hydroxyurea is FDA approved for melanoma but not clinically relevant.

b BRAFV600E mutation status unknown.
c Patient selection based on BRAFV600E mutation-positive tumor

ORR: overall response rate, OS: overall survival, DOR: duration of response, mOS: median overall survival, mPFS: median progression-free survival, HR: hazard ratio, CR: complete response, PR: partial response, ipi: ipilimumab.

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Preliminary clinical evidence

Merck submitted data from Trial P001 to support the breakthrough designation. Trial P001 was an ongoing, dose-escalation trial (Part A) with multiple activity-estimating cohorts (Parts A-1 and A-2, through F) in specified patient populations as listed below:

- Part A, A-1 and A-2: Dose escalation in advanced solid tumors
- Part B: Clinical activity/safety in advanced melanoma, ipilimumab-treated and -naïve
- Part C: Clinical activity/safety in non-small cell lung cancer (NSCLC) in patients with two prior therapies
- Part D: Dose finding in IPI-naïve advanced melanoma
- Part E: Dose finding/safety in combination with carboplatin/paclitaxel and cisplatin/pemetrexed in treatment-naïve patients with NSCLC, whose tumors express PD-L1 by immunohistochemistry (IHC) (cohort never initiated)
- Part F: Clinical activity/safety in patients with previously treated and treatment naïve nonsquamous NSCLC, whose tumors express PD-L1 by IHC.

The focus of the breakthrough therapy designation request was Part B of the trial. Part B consisted of patients with locally advanced or metastatic melanoma, either ipilimumab-naïve or previously treated with ipilimumab. Part B also included patients who are BRAF mutant and BRAF wild-type. BRAF mutant patients may have been previously treated with a BRAF or MEK inhibitor.

Per protocol, response rates were assessed by the investigator according to immune-related response criteria (irRC), with a justification that the patterns of response to treatment with immunotherapy agents differ from those with chemotherapy or targeted agent.\(^1\) However, Merck was also capturing response data using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, as determined by a centralized independent review, because response rates determined by irRC were considered exploratory.

Results

Preliminary results of the ongoing melanoma cohort (Part B), at the time of BTDR, are presented below. Included were all patients in Part B who received their first dose on or before April 25, 2012. All patients were dosed at 10 mg/kg every two weeks (n=57) or every three weeks (n=28).

Table 2 lists the overall response rate as determined by independent central review based on confirmed objective responses using RECIST 1.1 through December 3, 2012.\(^2\) A confirmed objective response was defined as a complete response or partial response evident on two consecutive CT scans performed at least four weeks apart. An overall response rate of 40% was observed in 85 melanoma patients. The response rates were 33% in ipilimumab-treated patients and 43% in ipilimumab-naïve patients. A complete response was observed in 3.5% of the melanoma patients, 3.4% in ipilimumab-naïve, and 3.7% in ipilimumab-treated patients. The median duration of response had not been reached; however, the range of duration of confirmed responses is 28 to 240+ days (8 months), with the longest duration of response of 4+ months in ipilimumab-treated patients and 8+ months in ipilimumab-naïve patients.

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Kaplan-Meier estimates of response duration for both ipilimumab-naïve and ipilimumab-treated patients were shown below in Figure 1 for confirmed objective responses.

Table 2. Best overall response in melanoma cohort (Part B) according to RECIST 1.1

<table>
<thead>
<tr>
<th></th>
<th>Objective Response (N, 95% CI)</th>
<th>Complete Response (N, 95% CI)</th>
<th>Duration of Response (days) Median (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All MEL</td>
<td>40% (34; 29% - 51%)</td>
<td>3.5% (3; 0.7% - 10%)</td>
<td>Not reached (28-240+)</td>
</tr>
<tr>
<td>N=85</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPI Naive</td>
<td>43.1% (25; 30% - 57%)</td>
<td>3.4% (2; 0.4% - 11.9%)</td>
<td>Not reached (30-240+)</td>
</tr>
<tr>
<td>N=58</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPI Treated</td>
<td>33.3% (9; 15% - 54%)</td>
<td>3.7% (1; 0.1% - 19%)</td>
<td>Not reached (20-169+)</td>
</tr>
<tr>
<td>N=27</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All patients dose at 10 mg/kg.
Includes all patients who received the first dose as of April 25, 2012.

Confirmed objective response is defined as a complete response or partial response that is evident on two consecutive CT scans obtained at least 4 weeks apart.

One additional patient (046) ipl-treated was reviewed by the imaging vendor on 07 Dec 12 and reported to have a confirmed partial response; confirmation will change to 35/85 (41%) overall and 10/27 (37%) in ipl-treated subgroup.

MEL=melanoma; IPI=ipilimumab

Figure 1. Kaplan-Meier estimates of confirmed response duration based on independent radiologist review for melanoma cohort (Part B)
Safety data were provided for 134 patients enrolled in Part B who started treatment before July 30, 2012 with a data cut-off date of September 28, 2012. Of these 134 patients, 113 were dosed at 10 mg/kg (Q2W n = 57, Q3W n = 56), and 21 patients were dosed at 2 mg/kg (Q3W). The most common adverse events (AEs), regardless of attribution, were fatigue, nausea, rash, diarrhea, cough, pruritus, arthralgia, and headache. The incidence of severe (Grade 3 or 4) AEs, regardless of attribution, was 26.9% (n=36), and the incidence of immune related AEs as reported by the investigators, was 15.7% (n=21).

Seven potentially immune-related Grade 3-5 AEs were reported by investigators (10 mg/kg): interstitial nephritis, pleuritic pain, pancytopenia, pneumonia/pneumonitis, abdominal pain/vomiting, hyperthyroidism, and hypothyroidism. Except for one case of pneumonia/pneumonitis and one case of abdominal pain/vomiting, all cases improved or resolved with supportive care and treatment with corticosteroids.

FDA Decision Determination

Within the past two years, two drugs, ipilimumab and vemurafenib, were approved for the treatment of metastatic melanoma based on demonstration of improved overall survival. Of these two, only vemurafenib demonstrated a high response rate (48%), and approval was restricted to the subset of patients with metastatic melanoma (approximately 50% of patients with cutaneous melanoma) whose tumors have a BRAF<sup>V600E</sup> mutation.

The Division determined that the preliminary evidence from Trial P001 indicated that pembrolizumab may demonstrate a substantial improvement over existing therapies for melanoma, as summarized below:

- confirmed overall response rate (ORR) of 40% (95% CI: 29%-51%), as assessed by independent central review (n=85 patients).
  - ORR of 33% in ipilimumab-treated patients (n=27)
  - ORR of 43% in ipilimumab-naïve patients (n=58)
- median duration of response had not been reached (range of confirmed responses of 28 to 240+ days).

On January 17, 2013, FDA granted breakthrough therapy designation to pembrolizumab for treatment of (1) unresectable or metastatic melanoma that is refractory to ipilimumab treatment and (2) unresectable or metastatic melanoma in patients who have not received prior ipilimumab therapy.
Breakthrough Therapy Designation: Exploring the Qualifying Criteria, Session II  
Case Study 2: Brigatinib

Breakthrough Therapy Designation Request Basics

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>ARIAD Pharmaceuticals, Inc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Brigatinib (AP26113)</td>
</tr>
<tr>
<td>Indication</td>
<td>The treatment of patients with anaplastic lymphoma kinase positive (ALK+) non-small cell lung cancer (NSCLC) that is resistant to crizotinib.</td>
</tr>
<tr>
<td>Division/Therapeutic Area</td>
<td>Division of Oncology Products 2, CDER, FDA</td>
</tr>
<tr>
<td>Date BTDR submitted</td>
<td>May 31, 2013</td>
</tr>
<tr>
<td>Initial BTDR denial (FDA)</td>
<td>July 29, 2013</td>
</tr>
<tr>
<td>Resubmission of BTDR</td>
<td>August 11, 2014</td>
</tr>
<tr>
<td>Date of BTDR grant</td>
<td>October 1, 2014</td>
</tr>
</tbody>
</table>

Overview

Disease description and intended population

Anaplastic lymphoma kinase (ALK) is a tyrosine kinase encoded on chromosome 2 that is primarily involved in developmental processes and expressed at low levels in adults (Camidge et al, 2012). Activating gene rearrangements, or mutations, in ALK (ALK+) have been identified as oncogenes in several different cancers, especially non-small cell lung cancer (NSCLC) (Camidge et al, 2012). The frequency of ALK rearrangements in the overall population of NSCLC patients ranges from 2% to 7%, which represents approximately 10,000 patients in the US each year and approximately 40,000 patients worldwide each year (Kwak et al, 2010; Wong et al, 2009).

Drug description and relevant regulatory history

Brigatinib (AP26113) is a novel, synthetic, orally-active tyrosine kinase inhibitor (TKI), discovered and developed by ARIAD Pharmaceuticals, Inc. (Cambridge, Massachusetts). In August 2011 crizotinib (Xalkori®, Pfizer, Inc.), an ALK inhibitor, received accelerated approval from the United States (U.S.) Food and Drug Administration (FDA) for the treatment of patients with locally advanced or metastatic NSCLC that is ALK+ as detected by an FDA approved test. This was the first ALK-inhibitor to receive FDA approval. The accelerated approval of crizotinib was based on two multinational, single-arm studies using response-rate endpoints (FDA Summary Basis of Approval for NDA 202570, 2011). In the June 2011 FDA “Guidance for Industry - Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics,” a “meaningful durable” objective response rate (ORR) was identified as a surrogate endpoint reasonably likely to predict clinical benefit in patients with advanced NSCLC.

In study 1 (N=136), with a median duration of treatment of 5.1 months, the ORR was 50% (95% CI: 42, 59) and the median duration of response was 11.3 months. In study 2 (N=119), with a median duration of treatment of 32 weeks, the objective response rate (ORR) was 61% (95% CI: 52, 70) and the median duration of response was 11.1 months (Xalkori Prescribing Information, 2014). The accelerated approval of crizotinib was granted with post-marketing requirements under 21 CFR 312 Subpart H that the clinical benefit of crizotinib be confirmed in two randomized phase 3 trials comparing treatment with crizotinib to single agent chemotherapy in the second-line setting (pemetrexed or docetaxel in PROFILE 1007; and to platinum-doublet in the first-line setting (pemetrexed plus cisplatin or carboplatin in PROFILE 1014) in patients with ALK+ NSCLC. Progression free survival (PFS) was the primary endpoint (FDA Summary Basis
of Approval for NDA 202570, 2011). In 2013, the positive results of PROFILE 1007, served as the basis for conversion from accelerated to traditional approval.

Despite representing a great therapeutic advance for ALK+ NSCLC, patients treated with crizotinib invariably develop resistance. In general, crizotinib resistance can be subdivided into primary and secondary resistance. The underlying reason for the failure of ALK+ NSCLC patients to achieve a response to crizotinib (primary resistance) is difficult to identify, but suboptimal inhibition of ALK is thought to be a contributing factor. The mechanisms underlying loss of response (secondary or “acquired” resistance) to crizotinib are becoming clearer (Camidge et al, 2012). Emerging data suggest that an important mechanism for acquired resistance is the emergence of point mutations in the kinase domain of ALK (Katayama et al, 2012). Mutations that confer resistance to crizotinib (such as the gatekeeper mutant L1196M, L1152R, G1269A, S1206Y, F1174L, D1203N, C1156Y, T1151Tins, and G1202R mutations) may act by reducing the binding affinity of crizotinib to ALK (Bang, 2012). Unlike EGFR secondary resistance where one mutation (T790M) is the dominant “gatekeeper”, there are many gatekeeper mutations associated with ALK+ secondary resistance. Other mechanisms of secondary resistance to crizotinib include the amplification of the ALK fusion gene and the activation of alternate signaling pathways (Camidge et al, 2012; Katayama et al, 2012). In all of these scenarios, a rational approach to overcoming resistance is the use of a more potent ALK inhibitor that retains activity against crizotinib-resistance mutations and that can also achieve target inhibition both systemically and in the CNS.

Summary of Clinical Evidence Submitted with the BTDR

Available therapies

The treatment landscape for ALK+ NSCLC significantly changed with the introduction of crizotinib and continues to evolve. In March 2013, the ALK-inhibitor ceritinib (Zykadia™, Novartis Pharmaceuticals Corp.) was granted breakthrough therapy designation for patients with metastatic ALK+ NSCLC previously treated with crizotinib. In September 2013, alectinib (F. Hoffmann-La Roche Ltd) was the second ALK-inhibitor to be granted breakthrough therapy designation, for the same population as ceritinib. Most recently, in April 2014, ceritinib received accelerated approval from FDA for the treatment of patients with ALK+ NSCLC who have progressed on or are intolerant to crizotinib. Like crizotinib, the trials supporting the accelerated approval of ceritinib utilized ORR as the primary efficacy endpoint, with Duration of Response (DOR) as a key secondary endpoint.

For patients who experience failure of crizotinib due to resistance or intolerance, ceritinib and chemotherapy are the only commercially available treatment options outside of clinical trials. However, the chemotherapy regimens commonly used for treatment of ALK+ NSCLC are not specifically approved for use in patients with ALK+ NSCLC and ceritinib has received accelerated approval, with the clinical benefit of treatment to be confirmed in further randomized trials. Thus, ceritinib is not, to date, considered available therapy.

In an unselected NSCLC population, first-line (doublet) chemotherapy typically yields an ORR of 30% (median PFS: 4.1 months) and second-line (single-agent) chemotherapy yields an ORR of <11% (median PFS: 2.9 months) (Shepherd et al, 2000; Fossella et al, 2000; Hanna et al, 2004; Shepherd et al, 2005; Kim et al, 2008; Shaw et al, 2012; Solomon et al, 2013). In patients whose disease has progressed on or is intolerant to crizotinib, an investigator-assessed ORR of 54.6% (95% CI: 47, 62) with a 7.4 month median duration of response was observed with 163 ALK+ NSCLC patients treated with ceritinib (Zykadia Prescribing Information, 2014).
In summary, for ALK+ NSCLC patients who have progressed on crizotinib (through either resistance or intolerance), available therapies are limited, and outcomes for these patients remain uncertain or unsatisfactory. Therefore, the population of ALK+ NSCLC patients who have progressed on crizotinib represents a considerable unmet medical need that could be addressed with a more potent TKI that offers improved responses, overcomes mutation-based resistance, and has stronger CNS activity.

**Preliminary clinical evidence**

Although brigatinib is still in development, the Company’s early conclusion is that the benefit:risk profile appears positive, and preliminary analyses from an ongoing phase 1/2 clinical trial described below provided early clinical evidence that brigatinib has the potential to offer a substantial improvement for patients with ALK+ NSCLC who have experienced failure with crizotinib therapy compared to chemotherapy ("available therapy" as defined in the May 2014 FDA Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics). Collectively, ARIAD’s assessment of the available therapy for crizotinib-resistant ALK+ NSCLC and data from the ongoing phase 1/2 trial below formed the basis and guided ARIAD’s decision to file a BTDR in 2013 (unsuccessful) and subsequent BTDR in 2014 (successful).

Brigatinib is currently being evaluated in two clinical trials: a phase 1/2 trial (AP26113-11-101, “101” NCT01449461) designed to assess the safety, tolerability, PK (steady-state plasma concentrations), and anti-tumor activity of brigatinib in cancer patients; and a pivotal phase 2 trial (AP26113-13-201, ALTA, NCT02094573) designed to assess the safety and efficacy (as determined by investigator-assessed ORR) in ALK+ NSCLC patients who progress on crizotinib treatment. The first patient was dosed in the 101 trial in September 2011 and recruitment was completed in July 2014, with a total of 137 patients enrolled. The first patient was dosed in the ALTA trial in June 2014, and recruitment is ongoing.

At the time of the initial BTDR submission in May 2013, a total of 55 patients were treated in the phase 1 portion of the 101 trial, with a total of 28 patients with ALK+ disease. Of the 16 evaluable ALK+ NSCLC patients who had received prior crizotinib and no other ALK inhibitors, 12 patients (12/16, 75%, 95% CI: 47.6, 92.7) had experienced a partial response. At the time of the analysis, information on confirmatory observations of responses at the subsequent time points ("a confirmed response") was not available. The preliminary responses appeared durable with the median time in response of 28 weeks (with the longest ongoing response at 40+ weeks). In addition, preliminary clinical CNS activity was observed in patients with ALK+ disease with brain metastases in the phase 1 portion of this study. Of five patients with ALK+ disease with active brain metastases at baseline and follow-up scans available, 4 had radiographic evidence of improvement. CNS lesion improvements in all four patients were ongoing, with durations ranging from 15 to 28+ weeks.

At the time of the subsequent BTDR submission in August 2014, a total of 125 patients had been treated with brigatinib in the 101 trial, with a total of 71 patients with ALK+ NSCLC. Of the 51 evaluable ALK+ NSCLC patients who had received prior crizotinib and no other ALK inhibitors, 35 patients (69%, 95% CI: 54.1, 81.9) experienced an objective response. Of the 57 evaluable ALK+NSCLC patients, 26 had confirmed responses, with four awaiting confirmation as of the extraction date. Response durations ranged from 1.6 to 14.7 months (ongoing) in patients with confirmed responses. Among 49 patients with follow-up scans, median progression-free survival by Kaplan-Meier estimate was 10.9 months. At the time of the analysis, of the 67 total ALK+ NSCLC patients, 50 (75%) remained on therapy. Furthermore, 14 patients (13 evaluable, 1 not evaluable) were identified with active brain metastases at the time of study entry. Nine of the 13 evaluable patients (69%) had regression of their brain metastases following treatment with brigatinib. The longest time on treatment of the 14 patients with brain
metastases was 85 weeks, and 11 of the 14 (79%) patients remained on study. In addition, improvement
in a patient with leptomeningeal metastasis was observed, which was reported as a confirmed complete
response.

**FDA Decision Determination**

FDA granted breakthrough status for the treatment of patients with metastatic ALK positive non-small
cell lung cancer (NSCLC) whose disease has progressed on or who are intolerant to crizotinib therapy.
The rationale behind the decision was that an ORR of 69% in over 50 previously crizotinib treated
patients (with a lower bound of 59%), which appeared to be durable (ongoing responses up to 15
months) along with supportive data of 100% ORR in the 6 crizotinib-naïve patients, and activity in the
CNS (a sanctuary site for crizotinib resistance) represented substantial improvement over available
therapy in a serious disease with high unmet medical need.

The preliminary adverse event profile appeared acceptable. The safety signal of pulmonary adverse
events appeared to be adequately investigated by the sponsor and pharmacovigilance measures were
instituted to further explore and characterize this risk. With the resubmission, Ariad provided ORR and
durability data in a larger cohort of patients to preliminarily exclude the response rate observed with
standard of care available therapies and to ensure that there was adequate follow-up to characterize
durability of response.

**Table 1: Pulmonary SAEs in patients treated with AP26113**

<table>
<thead>
<tr>
<th>SERIOUS ADVERSE EVENTS IN ≥ 3 PATIENTS</th>
<th>INCIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>7%</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>4%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>4%</td>
</tr>
<tr>
<td>Pulmonary Embolism</td>
<td>2%</td>
</tr>
</tbody>
</table>

12/125 (10%) of patients experienced dyspnea, hypoxia, dry cough, chest tightness, pneumonia, or pneumonitis

**References**

Bang YJ. Treatment of ALK-positive non–small cell lung cancer. Archives of Pathology & Laboratory


Center for Drug Evaluation and Research. Clinical Pharmacology and Biopharmaceutics Review:
Crizotinib, Application No. 202570Orig1s000. March 2011. Available at:


Hanna N, Shepherd FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in


Wong DW, Leung EL, So KK, et al. The EML4-ALK fusion gene is involved in various histologic types of lung cancers from nonsmokers with wild-type EGFR and KRAS. Cancer. 2009;115:1723–1733.


Proposed indication:
Hypothetix for the treatment of advanced unresectable or metastatic cancers of the hypothetical gland

April 24, 2015

Marc Theoret, MD
Clinical Team Leader, Melanoma and Sarcoma Team
Division of Oncology Products 2, Office of Hematology and Oncology Products

Contributor to Case: Gideon Blumenthal, MD
Clinical Team Leader, Thoracic and Head/Neck Oncology
DOP2, OHOP

Hypothetical Malignant Glandularomas (HMG)

• Heterogeneous group of solid tumors
• In 2014, 80,000 new cases and 20,000 deaths from HMG in the U.S.
  – 5-year survival:
    • Stage I: 95%, Stage II: 80%, Stage III: 30%, Stage IV: 5-15%
• Treatment options for advanced unresectable or metastatic disease
  – Single-agent chemotherapeutics
  – None demonstrated improved overall survival
# FDA-Approved Therapies for Metastatic HMG

<table>
<thead>
<tr>
<th>Drug (Approval Year)</th>
<th>Clinical Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo X (1970’s)</td>
<td>Tumor response rate of 10%</td>
</tr>
<tr>
<td>Chemo Y (1990’s)</td>
<td>Progression-free survival (PFS): - Median of 3.5 vs. 1.5 months - HR (95% CI): 0.4 (0.2, 0.5) - Tumor response rate: 20% vs. 8% - Duration of tumor response (95% CI) 5 months (3, 10)</td>
</tr>
</tbody>
</table>

## Hypothetix – Mechanism of Action / Rationale

- Monoclonal antibody that binds to HMG-associated protein X (HMG-X) and blocks the interaction with its ligand (HMG-XL)
- Blocking the interaction of HMG-X with HMG-XL modulates downstream signaling events
- Hypothetix decreases proliferation of HMG cell lines in vitro
- Hypothetix reduces tumor size in xenograft models of HMG – effect is substantially enhanced in combination with Chemotherapy Y
Clinical Data to Support BTD

- Open-label, international, RCT in patients with unresectable and/or metastatic HMG randomized (2:1) to receive as first-line therapy:
  - Hypothetix on Day 1 plus Chemotherapy Y on Day 1 of each 21-day cycle (n=80) OR
  - Chemotherapy Y on Day 1 of each 21-day cycle (n= 40)

- Primary Endpoint: Progression-free survival (PFS)
- Secondary Endpoint: Tumor response rate, duration of response (DOR), overall survival

### PFS and Tumor Response Rate

<table>
<thead>
<tr>
<th></th>
<th>Hypothetix + Chemo Y N=80</th>
<th>Chemo Y N=42</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression-free survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events, (%)</td>
<td>45 (56)</td>
<td>30 (71)</td>
</tr>
<tr>
<td>Median, mo. (95% CI)</td>
<td>5.1 (2.9, 8.6)</td>
<td>2.1 (1.4, 4.4)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.60 (0.4 – 0.95)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Tumor response Rate</td>
<td>20%</td>
<td>0</td>
</tr>
<tr>
<td>Median DOR, mo. (95% CI)</td>
<td>7.3 (3.4, 9.6)</td>
<td>--</td>
</tr>
</tbody>
</table>

No apparent difference in overall survival (OS): median 10.2 months versus 9.6 months, HR=0.94, p=0.72
Subgroup Analyses

- Retrospective testing to identify patients with HMG-XXL (high affinity variant of the ligand, ~25% of patients) demonstrated a median improvement in PFS of 8 months (HR 0.4) and similar tumor response rate with the Hypothetix combination.

- PFS subgroup analyses based on known prognostic factors for patients with HMG were not consistently in favor of the Hypothetix combination arm.

Safety

<table>
<thead>
<tr>
<th></th>
<th>Hypothetix + Chemo Y N=80</th>
<th>Chemo Y N=36</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>50%</td>
<td>25%</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>33%</td>
<td>10%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>30%</td>
<td>1%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>25%</td>
<td>8%</td>
</tr>
</tbody>
</table>
Division’s Recommendations

Denial: Preliminary clinical evidence does not demonstrate substantial improvement over available therapies

• Although a large relative effect on PFS, absolute magnitude relatively small
• Subset analysis retrospective and based on a small sample
• Add-on trial design: PFS improvement must be balanced with increased toxicities
• Control arm underperformed

Division’s Advice

• Conduct a new trial stratifying for presence of HMG-XXL and allocating appropriate alpha for this subgroup
• Meet with CDRH regarding validation of HMG-XXL assay prior to conducting the new trial
Breakthrough Therapy Designation Request Basics

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Novartis Pharmaceutical Corporation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Bimagrumab</td>
</tr>
<tr>
<td>Indication</td>
<td>Treatment of sporadic Inclusion Body Myositis (sIBM)</td>
</tr>
<tr>
<td>Division/Terapeutic Area</td>
<td>Division of Neurology Products, CDER, FDA</td>
</tr>
<tr>
<td>Date BTDR submitted</td>
<td>June 18, 2013</td>
</tr>
<tr>
<td>Date of BTDR grant</td>
<td>August 12, 2013</td>
</tr>
</tbody>
</table>

Overview

**Disease description and intended population**

sIBM is an acquired inflammatory and degenerative myopathy most common in patients above the age of 50 years (Badrising 2000). Prevalence estimates range from 10 to 70 per million in the US, approximately 3,000 to 20,000 patients. The etiology of sIBM is unknown. The disease is characterized by prominent weakness of the quadriceps and forearm flexors. Lower extremity symptoms include difficulty with rising from a chair and walking up- or down stairs, whereas upper extremity symptoms reflect grip weakness and decreased dexterity. Other affected muscle groups include the dorsiflexors of the ankle, causing foot/toe drop, the neck flexors and extensors, and the facial muscles. A distinct feature of sIBM is that weakness and atrophy are usually asymmetric, often more severely affecting the non-dominant side.

Disease progression is usually slow but irreversible, and most patients with sIBM require an assistive device, such as a cane, walker, or wheelchair within several years of onset (Griggs 1995, Dalakas 2006). Nearly all patients require considerable help with daily activities, and about 40% of patients are completely or severely dependent. Death secondary to sIBM occurs in some patients secondary to events such as aspiration pneumonia, immobility (deep vein thrombosis) or falls.

**Drug description and relevant regulatory history**

Bimagrumab (BYM338) is a fully human monoclonal antibody developed to stimulate muscle growth by binding competitively to activin receptor type IIB (ActRIIB) and IIA (ActRIIA) thus preventing natural ligands that inhibit muscle growth, such as myostatin, from binding. Bimagrumab is administered by intravenous infusion.

sIBM is associated with increased levels of SMAD 2/3 phosphorylation. It was hypothesized that inhibition of ActRII through bimagrumab could help improve muscle mass, strength, and function in patients with sIBM because SMAD phosphorylation reflects signaling through ligand-receptor pairs of the TGFB superfamily, and because ActRII is known to be important in such signaling in muscle (Amato 2014). There are no specific therapies for sIBM (Griggs 2006, Greenberg 2009). The mainstay of current treatment is supportive care.

Bimagrumab is not currently marketed for any indication in any country. Bimagrumab for the treatment of sIBM was granted fast-track designation and orphan drug designation in 2012. In addition to being developed for sIBM, bimagrumab is in clinical development for sarcopenia and hip fracture recovery.
**Summary of Clinical Evidence Submitted with the BTDR**

*Available therapies*

There are currently no approved drug therapies.

**Preliminary clinical evidence**

Preliminary clinical evidence supporting the breakthrough therapy designation came from a 24 week phase IIa single-dose (30 mg/kg) randomized, placebo-controlled, double-blind, parallel arm study of bimagrumab in 14 patients with sIBM.

The primary outcome was difference in thigh muscle volume (TMV) by MRI at 8 weeks. Secondary measures of clinical function were 6-minute walking distance (6MWD) and Timed Up and Go (TUG). Additional endpoints included isometric muscle strength measured by quantitative muscle testing (QMT), and lean body mass (LBM) assessed by dual-energy x-ray absorptiometry (DXA).

Eight weeks after dosing, the mean difference from baseline in TMV (right leg) favored bimagrumab (+7%; p=0.02). Left-leg TMV and whole LBM also favored bimagrumab (+8% and +6% respectively; nominal p=0.009 and p=0.01, respectively). In addition, a numerical increase in quadriceps muscle strength as measured by QMT was observed (Amato 2014).

A change favoring bimagrumab vs. placebo on 6MWD was observed 16 weeks after the single administration, (+15%; nominal p=0.008). This represented a +49 m difference from placebo in 6MWD in patients treated with bimagrumab. A review of change from baseline to Week 16 in 6MWD for individual patients showed a generally consistent increase in the BYM338 group, and decrease in the placebo patients. TUG results did not show a difference between treated and control patients.

Other evidence considered included:

- **Pharmacodynamic effect**: positive findings for thigh muscle volume in separate studies in healthy volunteers.
- **Comparison to natural history**: Increase in 6MWT observed in the phase IIa study vs. decrease expected from natural history (about -30 m/year).

**FDA Decision Determination**

In sIBM, impaired walking is a key symptom. 6MWD represents a direct measurement of patients walking ability and as such, is a clinically relevant endpoint in sIBM. Phase IIa data on 6MWD suggested potential for a large, consistent increase in walking ability in sIBM patients. Comparison of treatment arm to a randomized control group and to natural history was possible. The clinical observation was supported by consistent tissue/organ-level biomarker findings, including increased muscle volume, within the same patients. External evidence of pharmacodynamic effect on muscle was provided by studies in healthy volunteers. There was an overall high (but not absolute) level of consistency across data.

**References**

Breakthrough Designation
Hypothetical Denial Case Study:
Neurology Drug

Breakthrough Therapy Designation: Exploring the Qualifying Criteria
April 24, 2015, Washington DC

Ronald Farkas, MD, PhD
Clinical Team Leader
Division of Neurology Products
Office of New Drugs/CDER/FDA

Disease, Indication, Drug

- Disease:
  - Fulfills criteria for "serious or life-threatening"
  - Unmet medical need exists; no approved drugs

- Indication
  - Rare neurological disease, childhood onset
  - 5,000 affected individuals in U.S.
  - Characterized by progressive weakness
  - Respiratory insufficiency in adulthood
  - Shortened life-span

- Drug: Intended to slow disease progression
  - Pharmacodynamic effect based on genetic defect
Acceptable Endpoints

- Ability to perform daily activities
  - e.g. walking ability, patient-reported ADL’s
- Symptoms
  - e.g. shortness of breath
- Decrease in secondary complications
  - e.g. hospitalizations due to pneumonia
- Survival
- Other clinical endpoints may be acceptable
- Most biochemical surrogates in this case problematic because pathophysiology poorly understood

Study Design

- 16-week, randomized, placebo-controlled
- High dose / low dose / placebo
- 30 patients randomized 1:1:1
- Primary Endpoint
  - Biochemical marker of pharmacodynamic effect; not a clear surrogate
- Secondary
  - Pulmonary function tests
  - Hand-held dynamometry
  - Disease-specific patient-reported outcome
  - Timed walk
Preliminary Clinical Evidence

• Some differences across arms in baseline characteristics, such as age and strength
• Low dose: no evidence of efficacy
• High dose
  – Primary biomarker endpoint: negative
  – Clinical endpoints
    ▪ Hand held dynamometry: p = 0.02
    ▪ Timed walk: p = 0.07
    ▪ Patient-reported outcome: p = 0.24
    ▪ Functional vital capacity: numerically inferior

Preliminary Clinical Evidence-2

• If select half of patients with less severe baseline severity
  ▪ Hand-held dynamometry: p = 0.006
  ▪ Timed walk: p = 0.01
  ▪ Patient-reported outcome: p = 0.13
  ▪ Vital capacity: p = 0.03
Sponsor Conclusions

- Biomarker findings
  - Negative due to technical factors; non-contributory
- Positive clinical findings support designation
  - Study suggests dynamometry the best endpoint
- Subset analysis
  - Supported by drug mechanism and pathophysiology
  - Highly statistically significant
  - Multiple positive endpoints confirm efficacy

FDA Considerations

- Negative biomarker
  - *Increases concern that drug may not have intended pharmacodynamic effect*
- Problematic to try to ‘rescue’ negative study by considering *Clinical endpoints* if *biomarker* negative or *Biomarker endpoints* if *clinical primary* negative
  - When data very limited, consistency of findings critical
Clinical Endpoint Considerations

• Reasonable to design phase 2 study to learn about clinical endpoint performance
  ▪ Consistent with overall exploratory goals
• But inflation of type 1 error from multiple-testing no less a factor
  ▪ Multiplicity a concern even for pre-specified primary if statistical analysis not clearly pre-specified
  ▪ No reliable way to determine if nominally positive results due to chance
  ▪ Endpoints that lean against efficacy very worrisome

Clinical Endpoint Considerations-2

• Post-hoc subsets may appear reasonable, but multiplicity a dominant factor
  ▪ e.g. if results had favored more advanced patients, similar argument could be made
  ▪ Even very small p-values not interpretable
• “Consistency of findings” across endpoints can arise even when drug ineffective, e.g.
  – Endpoints can measure same difference between arms that arose by chance, for example from baseline imbalances
    ▪ Common in small studies (and subsets of small studies)
  – Other “true” differences that arise from non-random dropout, unblinding, etc
Breakthrough Therapy Designation Request Basics

<table>
<thead>
<tr>
<th>Sponsor:</th>
<th>GlaxoSmithKline and Medicines for Malaria Venture (MMV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug:</td>
<td>Tafenoquine</td>
</tr>
<tr>
<td>Indication:</td>
<td>Tafenoquine (TQ) will be indicated for the treatment and radical cure (relapse prevention) of <em>Plasmodium vivax</em> malaria</td>
</tr>
<tr>
<td>Division/Therapeutic Area:</td>
<td>Division of Anti-Infective Products, CDER, FDA</td>
</tr>
<tr>
<td>Date BTDR submitted:</td>
<td>October 31, 2013</td>
</tr>
<tr>
<td>Date of BTDR grant:</td>
<td>December 18, 2013</td>
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</table>

Overview

*Disease description and intended population*

*Plasmodium vivax* (*P. vivax*) malaria is a neglected tropical disease and a major cause of uncomplicated malaria (~50% cases malaria worldwide). *P. vivax* malaria has significant economic impact primarily in South & South East Asia, Latin America and the horn of Africa, where the majority of the estimated 130-390 million annual clinical cases occur. The global cost of treating malaria to health systems has been estimated at between US $0.9 and $2.7 billion per year, while the cost to individuals from lost productivity (each episode of *P. vivax* results in absence from school or work) and other costs, has been estimated at between $1.4 and $4.0 billion per year. In addition, recent evidence suggests that the severity of disease that can be caused by *P. vivax* has been underestimated. *P. vivax* has been shown to cause severe anemia, respiratory distress, malnutrition and death.

As a reflection of this, the World Health Organisation (WHO) has recently announced the development of a global vivax strategy to control and eliminate this relapsing form of malaria. The development of such a strategy recognizes the fact that success of global malaria eradication efforts will to a large extent depend on the ability to combat this particular, geographically widespread parasite.

*P. vivax* has a complex lifecycle which includes a dormant liver stage; the hypnozoite. Hypnozoites are formed immediately after infection of the human host, and their activation leads to the re-appearance of clinical symptoms of malaria (relapse) normally for up to several months after the initial infection. Conversely, infection with *P. falciparum* does not result in relapse, as the parasite lifecycle does not include a hypnozoite stage. Additionally the presence of hypnozoites allows *P. vivax* to be prevalent in temperate regions, when the insect vector is not present at all times of the year. Consequently, 40% of the world’s population is threatened by *P. vivax*. Hypnozoite activation patterns are felt to be adapted to the climatic conditions in malaria-endemic areas. *P. vivax* responds less well than *P. falciparum* to classical malaria control measures, such as vector control and bed net distribution. In areas where both parasites co-exist and with control measures applied, relative prevalence of *P. vivax* has been shown to increase. Therefore, tackling the reservoir of dormant hypnozoites is a key scientific challenge for ongoing malaria eradication efforts.

*Drug description and relevant regulatory history*

Tafenoquine (TQ, SB-252263 and WR 238605), is a new 8-aminoquinoline anti-malarial drug being co-developed by GlaxoSmithKline (GSK) and the Medicines for Malaria Venture (MMV) with the assistance
and historic support of the Walter Reed Army Institute of Research. It is a synthetic analogue of primaquine (PQ). TQ has been shown to be effective in the treatment of plasmodial infections in vitro, and also in preclinical models in vivo and during early phase clinical studies. To date, TQ has shown to be well-tolerated in clinical studies in >4000 subjects under a variety of development programs including malaria chemoprophylaxis, post-exposure prophylaxis in addition to *P. vivax* treatment, and relapse prevention studies. Of note, TQ possesses activity against all stages of the *Plasmodium* lifecycle, including the dormant *P. vivax* hypnozoite. GSK has an active Investigational New Drug Application (IND) for studies in *P. vivax* malaria with the Division of Anti-Infective Products, Office of Antimicrobial Products, FDA. Clinical studies are being conducted under the IND. The objectives of the clinical development program are to determine the safety and efficacy of TQ as a combination treatment with a blood schizonticidal drug to achieve radical cure of *P. vivax* malaria. Previous studies with TQ have been conducted under IND sponsored by the U.S. Army Medical Material Development Activity (USAMMDA) in collaboration with GSK.

Clinical studies with TQ are being conducted internationally in countries where a high incidence of *P. vivax* infection exists. Appropriate regulatory filings including Clinical Trials Applications and Ethics Committee reviews have been pursued for Thailand, Brazil, Bangladesh, Peru, Philippines and India. A phase 2b dose-ranging study for TQ (TAF112582, Part 1) was conducted in India, Thailand, Brazil and Peru.

In the U.S., tafenoquine has been granted an orphan-drug designation for the treatment of malaria by the FDA on January 15, 2013 (Designation Request #12-3858).

**Summary of Clinical Evidence Submitted with the BTDR**

*Available therapies*

There is a need to provide alternative treatments to manage vivax relapse over and above PQ, which is the only treatment approved in the US for the radical cure (prevention of relapse) of vivax malaria. PQ is administered as a once-a-day oral dose for 14 days and it is widely accepted that the long dosing leads to reduced compliance and hence reduced clinical efficacy. As such, alternative treatments with less frequent dosing regimens are necessary. TQ has the potential to provide alternative treatment which can be administered as a single dose thereby resulting in improved compliance and expected improvement in serious negative outcomes associated with *P. vivax* infections. Co-administration with another blood schizonticide (chloroquine) will be required for treatment of *P. vivax* malaria as this combination targets both blood and liver stages of infection.

*Preliminary clinical evidence*

The clinical data presented in this section include efficacy data from a recently completed Phase 2b clinical study (TAF112582) for the treatment of *P. vivax* in adults and supporting efficacy evidence from two additional studies.

**Study TAF112582**

Part 1 of study TAF112582 was conducted between September 2011 and March 2013 in order to identify a safe and efficacious dose of tafenoquine which, when co-administered with chloroquine, effectively prevents relapse of *P. vivax* malaria. The study design is illustrated below:
The study recruited 329 subjects from Peru (136), Brazil (37), Thailand (99) and India (57). Ninety-seven percent (97%) of subjects completed the 6 month follow-up. Analysis of the primary efficacy endpoint (relapse free efficacy by malarial slide read) showed convincing efficacy for the tafenoquine 300mg and 600mg doses which remained consistent when sensitivity analyses were performed using different analysis populations and methodologies. Results from the primary analysis are shown below. The magnitude of treatment effects relative to the chloroquine control far exceeded the defined clinically relevant threshold of 30%. A plot of Kaplan-Meier estimates is also shown illustrating the tafenoquine dose-response and how efficacy over time compares to the chloroquine control arm and the current standard of care (PQ).
Kaplan-Meier Survival Curves show dose response over 6 months for TQ compared to control arms.

There were no emergent safety signals of concern noted in this study:

- The majority of the hemoglobin (Hb) declines were mild and distributed across all treatment groups with no discernible dose-related trends.
- There were 29 SAEs in the study: most were QT prolongations that were distributed across most treatment groups (notably not observed in TQ 600 mg arm) with no additional effect of TQ seen over the expected CQ effect.
- AEs occurring at a frequency of >12% were symptoms associated with episodes of malaria recurrence.

The preliminary clinical evidence of efficacy presented for the treatment of *P. vivax* in adults from the Phase 2b clinical study (TAF112582) supports that TQ may provide substantial improvement over existing therapies in the treatment and radical cure of *P. vivax* malaria. In conclusion, TQ 300mg or 600mg, as a single-dose treatment co-administered with chloroquine effectively prevents *P. vivax* relapse. 300mg has been selected for phase 3 development as it offers a lower potential hemolytic risk than 600mg in patients with G6PD deficiency with no reduction in efficacy. Although the study was not designed to test superiority of TQ to PQ, the efficacy rate for TQ 300mg was 12% higher than for PQ. The phase 3 program will generate efficacy and safety data from 500 subjects treated with TQ 300mg and 250 subjects treated with PQ. A meta-analysis of the phase 2b and phase 3 studies will be performed to directly compare efficacy of TQ and PQ.
Supportive Historical Clinical Studies

Two studies exploring TQ in the *P. vivax* infection were conducted in Thailand by GSK with the Armed Forces Research Institute of Medical Sciences (AFRIMS), under US Army IND 038503.

**Study SB-252263/047**

Study SB-252263/047 was a randomized, open label, dose ranging study to investigate the safety and efficacy of TQ in the prevention of relapse of *P. vivax* infection in Thailand. The primary objective was to investigate the efficacy of various dosing regimens of TQ when used in combination with the blood schizonticide, CQ in order to determine an optimal dose for the phase 2b study TAF112582. A total of 124 subjects were enrolled into 9 treatment arms (7 dose regimens of TQ ranging from total doses of 500mg to 3000mg, PQ and CQ alone). The study demonstrated that when administered sequentially after CQ, the TQ relapse rate was between 0% and 13%. There were a total of 3 relapses across the TQ arms of 69 patients dosed (4%), 12/17 (71%) in the CQ arm and 3/12 (25%) in the PQ arm. In conclusion, this study successfully provided proof of concept for the treatment of *P. vivax* malaria with TQ and CQ. Low doses of TQ prevented malaria relapses in this study conducted in Thailand.

**Study SB-252263/058**

SB-252263/058 was a randomized, active control, double blind, double dummy phase 2 study to evaluate the treatment of acute *P. vivax* and the prevention of *P. vivax* relapse in Thai subjects. Subjects received either a TQ dose of 400 mg daily for 3 days (N=46) or the standard regimen of CQ + PQ (15mg x 14 days) (N=24). TQ was given as a monotherapy treatment in this study: a second blood schizonticide was not administered.

TQ demonstrated significant schizontocidal activity as 93.0% of subjects in the TQ PP population achieved an adequate clinical response. However, a three day dosing regimen of 400 mg TQ per day did not achieve the primary endpoint (lower limit of the 2-sided 90% confidence interval no less than 85%) and therefore did not meet the pre-defined efficacy threshold for the treatment of acute *P. vivax* malaria in this study. TQ was highly efficacious (100% relapse-free efficacy) for up to 120 days. The PQ+CQ regimen achieved 95% efficacy. However, the TQ monotherapy regimen exhibited slow parasite and fever clearance times relative to the CQ+PQ control. Therefore, this study concluded that TQ needed to be co-administered with a fast acting blood schizonticide such as CQ, which is the basis for the current clinical program.

**FDA Decision Determination**

The Agency’s decision to grant Breakthrough Therapy Designation for tafenoquine for treatment and radical cure of vivax malaria was based on the fact that it has been developed for a serious infection and on a review of the efficacy results of the phase 2 trials which are discussed above. Breakthrough designation was granted on 12/18/2013. During the review period, the Division of Anti-Infective Products met with the Sponsor on 11/17/2013 for an end-of-phase 2 meeting to discuss phase 2 trial results and the Sponsor’s proposed phase 3 clinical development program. As per Agency policy, the Division of Anti-infective Products briefed members of the Center for Drug Evaluation and Research (CDER) Medical Policy Council on the rationale for Breakthrough Therapy Designation for tafenoquine. The preliminary clinical evidence of efficacy for the treatment of *P. vivax* in adults from the Phase 2b clinical study (TAF112582) presented supports that TQ may provide substantial improvement over primaquine in the treatment and radical cure of *P. vivax* malaria. Tafenoquine provides an alternative treatment with a shorter dosing regimen; it is administered as a single-dose which should improve patient compliance and could reduce complications associated with *P. vivax* infection.
Breakthrough Therapy Designation: Exploring the Qualifying Criteria, Session IV
Case Study 7: NaBen

Breakthrough Therapy Designation Request Basics

<table>
<thead>
<tr>
<th>Sponsor:</th>
<th>SyneuRx International (Taiwan) Corp.</th>
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<tr>
<td>Drug:</td>
<td>NaBen (SND13)</td>
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<td>Indication:</td>
<td>Adjunctive therapy for schizophrenia</td>
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<td>Division/Therapeutic Area:</td>
<td>Division of Psychiatric Products, CDER, FDA</td>
</tr>
<tr>
<td>Date BTDR submitted:</td>
<td>October 10, 2014</td>
</tr>
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<td>Date of BTDR grant:</td>
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Overview

Disease description and intended population
Schizophrenia is a chronic debilitating mental illness with high levels of associated morbidity and mortality. It is characterized by positive symptoms (hallucinations, delusions and disorganized thoughts), negative symptoms (flat affect, anhedonia, ambivalence, and amotivation), and cognitive deficits (generally associated with memory, judgment, and executive planning). It is also among the top disabling conditions worldwide, affecting an estimated 1% of the total world population. The typical onset of schizophrenia is during the late adolescence and early adulthood. Patients with schizophrenia go on to struggle with lifelong functional impairments, lack of independent living skills, and difficulty with social functioning, including severe problems with social, educational and occupational performance.

While the positive symptoms are striking, they are relatively treatable. Research suggests that the negative symptoms of schizophrenia, including problems with motivation, social withdrawal, diminished affective responsiveness, speech, and movement contribute more to poor functional outcomes and quality of life (QOL) for individuals with schizophrenia than do the positive symptoms. Therefore, negative symptoms of schizophrenia are a serious condition and clinically important target for new drug development due to their profound effect on an individual’s ability to function socially or vocationally. Furthermore, individuals living with schizophrenia and other long-term psychoses report worse health-related QOL compared to the general population of patients with physical illness. The US national health cost of schizophrenia is estimated to be at 2.5-3% of the total expenditure.

Drug description and relevant regulatory history
Recent research suggests dysfunction in the hypofunction of the glutamate N-methyl-D-Aspartate receptor (NMDAR) may have an important role in the pathophysiology of schizophrenia. Enhancing NMDAR-mediated neurotransmission is considered a novel treatment approach in improving schizophrenia associated symptoms. To date, several trials of adjuvant NMDA-enhancing agents, including D-amino acid (DAA) co-agonists (glycine, D-serine, D-alanine), as well as glycine transporter-1 inhibitors (sarcosine and bitopertin), have revealed suggestive, but limited, efficacy for positive and negative symptoms as well as cognition. An alternative method to enhance NMDA function is to raise the levels of DAA by reducing their metabolism via DAAO inhibitor.

NaBen® (sodium benzoate) is a D-amino acid oxidase (DAAO) inhibitor with a well-developed safety profile. Sodium benzoate is a well-known food preservative approved by the World Health Organization.
(WHO), United States of America (USA), European Union (EU), Japan, and Taiwan. NaBen® is formulated as a white oral tablet (sodium benzoate, 500 mg) that can be taken at a total dose of 1000 mg/day as an adjunctive therapy for schizophrenia.

The NaBen® treatment is a breakthrough treatment since there is no approved adjunctive treatment for this serious medical condition. In addition, NaBen® has received the FDA orphan product designation for the indication of schizophrenia in the pediatric population and has a phase IIb/III study for Schizophrenia in Adolescents currently ongoing (IND 119256).

Summary of Clinical Evidence Submitted with the BTDR

Available therapies

The dopamine hypothesis has dominated the thinking about pathophysiology and has been the basis of all pharmacological treatment of schizophrenia for nearly 50 years. However, dopamine blockade through conventional antipsychotics (Chlorpromazine, Haloperidol, Perphenazine, etc.) mostly affects the positive symptoms of schizophrenia. Newer atypical antipsychotics (Aripiprazole, Paliperidone, Clozapine, etc.) target both dopamine (D2 antagonists) and serotonin receptors (5HT2A agonists). However, there are still a considerable percentage of patients whose positive symptoms are resistant to or only partially responsive to available treatments. There are no medications that address the negative or cognitive aspects of the illness. Moreover, the adverse-effect profiles of the typical and atypical antipsychotic agents are severe and include hypotension, seizure, sedation, weight gain, hyperglycemia, diabetes mellitus, hyperlipidemia, potentially fatal neuroleptic malignant syndrome and extrapyramidal symptoms, risk of stroke in the elderly, and hematological abnormalities.

Preliminary clinical evidence

Preliminary evidence to support NaBen® treatment is from a trial using a double blind, placebo-controlled adjunctive design and results can be found in Lane HY, et al. JAMA Psychiatry. 2013;70:1267-75. Benzoate produced a 21% improvement in PANSS total score and large effect sizes (range, 1.16-1.69) in the PANSS total and subscales, Scales for the Assessment of Negative Symptoms–20 items, Global Assessment of Function, Quality of Life Scale and Clinical Global Impression. Furthermore, there were also significant improvements in the neurocognitive subtests of Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB). The benzoate group was better in speed of processing (P = .03, ES = 0.65) and visual learning and memory (P = .02, ES = 0.70). Benzoate was well tolerated without significant adverse effects.

Additional factors

Since no therapy has proven improvement on negative symptoms, the appropriate endpoint is unclear. The negative symptom subscale of the PANSS has been able to identify this disorder but experts have raised doubts about its appropriateness as an endpoint based on epidemiological factor analysis and may need refinement. The SANS and the NSA-16 have both been proposed. Also, the effect on the PANSS score was larger than what is typically observed in regular treatment trials.

FDA Decision Determination

The division has previously outlined an approval pathway in a publication (Laughren T, Levin R. Food and Drug Administration perspective on negative symptoms in schizophrenia as a target for a drug treatment claim. Schizophr Bull. 2005;32:220–222). It is clearly stated that if a therapy improved all aspects of the illness, it would be considered a “broad” treatment of schizophrenia. The supportive single study, Lane HY et al., which the investigator submitted with the packet, clearly improves positive, negative and cognitive symptoms of the illness. Therefore, the agency contacted the sponsor and suggested that the
proposed indication be expanded to the adjunctive treatment of schizophrenia indication. This area is clearly an unmet clinical need and patients would greatly benefit from having medication that would improve not only the positive symptoms but the whole syndrome.
### Breakthrough Therapy Designation Request Basics

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<tr>
<th><strong>Sponsor:</strong></th>
<th>bluebird bio, Inc.</th>
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<tr>
<td><strong>Investigational Product:</strong></td>
<td>LentiGlobin BB305 Drug Product (autologous CD34+ hematopoietic stem cells transduced with LentiGlobin BB305 lentiviral vector encoding for the βA-T87Q-globin gene)</td>
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<td><strong>Indication:</strong></td>
<td>Treatment of transfusion dependent patients with β-thalassemia major</td>
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<td><strong>Division/Therapeutic Area:</strong></td>
<td>Office of Cellular, Tissue, and Gene Therapies (OCTGT, CBER, FDA)/Hemoglobinopathy</td>
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<tr>
<td><strong>Date BTDR submitted:</strong></td>
<td>December 2012 (denied)</td>
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<tr>
<td><strong>Resubmission of BTDR:</strong></td>
<td>December 2014</td>
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<td><strong>Date of BTDR grant:</strong></td>
<td>February 2015</td>
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### Overview

**Disease description and intended population**

β-thalassemia is a hereditary blood disorder which is rare in the United States (U.S.) and found most commonly in persons of Mediterranean, Middle Eastern, Indian, and Southeast Asian descent. β-thalassemia is a severely debilitating condition which can be life-threatening. The condition is caused by the absence or reduced production of the β-globin chains of hemoglobin A (HbA). Patients with the most severe form of the disease, β-thalassemia major, require regular blood transfusions to survive. However, even with regular transfusions and concomitant iron chelation therapy (the standard of care), the average life expectancy for a patient with β-thalassemia major is reduced by decades and patients are burdened with significant quality-of-life issues and morbidities associated with the condition.

**Drug description and relevant regulatory history**

LentiGlobin BB305 Drug Product (DP) is a gene therapy product developed to treat patients with β-thalassemia major. LentiGlobin BB305 DP consists of autologous CD34+ hematopoietic stem cells (HSCs) transduced ex vivo with the LentiGlobin BB305 lentiviral vector (LVV) encoding functional human βA-T87Q-globin. Expression of βA-T87Q-globin can be measured in peripheral blood and is expected to improve the β-globin/α-globin imbalance in differentiated erythrocytes containing the βA-T87Q-globin gene, enhance erythropoiesis, and thereby reduce or eliminate transfusion dependence in patients with β-thalassemia major.

A first BTDR for LentiGlobin BB305 Drug Product for the treatment of β-thalassemia was submitted to FDA OCTGT before the FDA guidance on Expedited Programs for Serious Conditions was published. This first application contained a summary of nonclinical studies comparing LentiGlobin HPV569 LVV (a predecessor vector of LentiGlobin BB305 LVV) and LentiGlobin BB305 LVV, and clinical evidence on 3 subjects treated with LentiGlobin HPV569 DP in clinical study LG001. LentiGlobin HPV569 DP consists of autologous CD34+ hematopoietic stem cells transduced with LentiGlobin HPV569 LVV. Both LVVs encode for the βA-T87Q-globin gene and share the same internal globin promoter and Locus Control Region, which together drive expression exclusively in the erythroid lineage.
In clinical study LG001, three subjects were treated with LentiGlobin HPV569 DP. One subject became transfusion independent by 1 year post-transplant (Cavazzana-Calvo et al., 2010) and remained transfusion-free through 5 years post-transplant, one subject did not engraft and received back-up cells, and one remained transfusion dependent.

This original request was denied because no clinical data with LentiGlobin BB305 DP were available. A revised BTDR with the clinical evidence described below was submitted subsequently, and BTD was granted earlier this year.

**Summary of Clinical Evidence Submitted with the BTDR**

**Available therapies**

The only currently available potential cure for β-thalassemia is allogeneic hematopoietic stem cell transplant (allo-HSCT). Allo-HSCT is rarely used and is primarily limited to patients with a human leukocyte antigen (HLA)-matched sibling donor and can be associated with significant mortality and morbidity. Thus, the vast majority of patients with β-thalassemia major receive conventional standard of care described above (chronic transfusions and iron chelation). Given the severity of the disease and lack of suitable treatment options, β-thalassemia major remains a devastating disease with a significant unmet medical need.

**Preliminary clinical evidence**

The rationale for using LentiGlobin BB305 DP in the treatment of β-thalassemia major is based on several observations: 1) preclinical results showing correction of disease in a mouse model of β-thalassemia treated with syngeneic cells transduced ex vivo with LentiGlobin BB305 LVV, 2) preliminary clinical evidence demonstrating a substantial benefit over existing therapies (as evidenced by rapid and sustained \( \beta^{A-T87Q} \)-globin production and alleviation or reduction of subject’s pre-treatment transfusion requirements after LentiGlobin BB305 DP treatment), and 3) anticipated alleviation of the limitations (primarily the need to have an HLA-matched sibling donor) and risks (primarily graft rejection and graft-versus-host disease [GVHD]) associated with allo-HSCT by the use of genetically modified autologous cells.

As of 30 November 2014, 7 subjects with β-thalassemia major, including \( \beta^0/\beta^E \), \( \beta^0/\beta^0 \) and \( \beta^0/\beta^+ \) genotypes, had been treated with LentiGlobin BB305 DP in Studies in HGB-204 (N=5) and HGB-205 (N=2). Preliminary clinical evidence in these subjects at the time of the BTDR application, demonstrated a rapid production of HbA containing \( \beta^{A-T87Q} \)-globin (HbA\(^{T87Q}\)) resulting in minimal to no transfusion support in less than 3 months post-treatment for previously transfusion-dependent β-thalassemia patients (studies HGB-204 and HGB-205). This result was observed in all subjects treated at the time of BTDR with at least 3 months of follow-up (4 of 4). These early data represent the potential for efficacy with rapid transfusion independence with near normal levels of hemoglobin seen in multiple subjects, coupled with consistent production of \( \beta^{A-T87Q} \)-globin indicating the cause of the transfusion independence is due to treatment with LentiGlobin BB305 DP.

At the time of the BTDR, the safety profile of LentiGlobin BB305 DP was also consistent with myeloablative conditioning used for autologous transplantation. No ≥ Grade 3 drug product-related adverse events had been observed and results of integration site analyses showed highly polyclonal reconstitution. No serious adverse events considered by the investigator to be related to LentiGlobin BB305 DP had been reported in Studies HGB-204 or HGB-205.
Thus, LentiGlobin BB305 DP was demonstrated to have the potential to address a significant unmet medical need in the treatment of β-thalassemia major by addressing the underlying cause of the disease. LentiGlobin BB305 DP has the potential to decrease or eliminate the transfusion dependence (and the consequent iron-overload morbidity) of patients with β-thalassemia major, but without the requirement of finding a matched donor and with reduced risk of transplant-related mortalities, GVHD and graft rejection.

LentiGlobin BB305 DP for the treatment of β-thalassemia major represents a substantial improvement over available therapy, as evidenced by preliminary clinical data demonstrating transfusion independence. Substantial improvement was based on the fact that reversion to transfusion independence does not occur spontaneously in nature in patients with β-thalassemia major. LentiGlobin BB305 DP therefore met the qualifying criteria for designation as a Breakthrough Therapy, as enacted as part of Section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) on July 9, 2012.

**FDA Decision Determination**
Considerations for clinical evidence in rare diseases, such as β-thalassemia, are different than in common diseases (magnitude of effect, rather than formal statistical analyses). Gene therapy products are often modified during clinical development prior to Phase 3. Establishing comparability between different versions of the product can be challenging.

**Reference**