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Breakdowns In The Breakthrough Lane: When Recipients Of FDA Expedited Designation Fall Short

by Bridget Silverman

Safety signals were the most common cause of discontinued candidates in the breakthrough therapy designation program in 2023.

Eiger BioPharmaceuticals, Inc.'s peginterferon lambda, *Gilead Sciences, Inc.*'s magrolimab, *Takeda Pharmaceutical Co. Ltd.*'s TAK-994 and *Bavarian Nordic A/S*'s RSV vaccine are the latest entrants to the small group of products that received breakthrough therapy designations but went on to struggle with clinical failure, changing strategic priorities, and regulatory missteps.

The BTD program is a success by most any measure. The Pink Sheet US FDA Performance Tracker has identified close to 500 designations granted since BTD was introduced in 2015. Nearly 60% have gone on to approval. Another quarter are in clinical development. Applications for approval from 20 BTD programs are currently under FDA review.

Almost 40 complete response letters have been issued to BTD products. Nearly 40% have since been approved. [*For more details on BTDs, supporting data and current clinical status, see the Pink Sheet FDA Performance Tracker's Breakthrough Therapy Designations chart*.]

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An unlucky 13 BTD programs later lost the designation to FDA rescission or voluntary withdrawal. Close to 40 programs have been disclosed as discontinued or suspended.

Given that they account for less than 10% of BTDs awarded, the absolute number of discontinued programs is always small, but it is notable that nearly 60% of discontinuations and suspensions came in the last three and half years, with a little over 40% in the five years before 2020.

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Safety Findings

Safety signals emerging during clinical trials were the most common reason for BTD product discontinuations this year, causing Eiger, Gilead and Takeda to stop development programs.

Eiger announced the discontinuation of the Phase III LIMT-2 trial of peginterferon lambda in chronic hepatitis delta on 12 September 2023 after four patients had hepatobiliary events that resulted in liver decompensation.

Eiger has received five breakthrough therapy designations for its portfolio of rare disease and virology therapies, resulting in one approved product – Zokinvy (lonafarnib) for progeria. After a portfolio review, however, only Zokinvy and the GLP-1 antagonist avexitide for hyperinsulinemic hypoglycemia indications remain priorities, Eiger announced on 29 June. (Also see "*Finance Watch: FibroGen, Amarin And Others Downsize To Survive*" - Scrip, 19 Jul, 2023.)

Gilead discontinued the Phase III ENHANCE trial of anti-CD47 monoclonal antibody magrolimab in first-line higher-risk myelodysplastic syndrome due futility in an interim analysis in July.

Newly diagnosed MDS was the only BTD awarded to magrolimab, which is also being studied in the pivotal ENHANCE-2 study in acute myeloid leukemia with TP53 mutations and ENHANCE-3 trial in first-line unfit AML. On 21 August, however, Gilead announced a partial clinical hold on the AML program. (Also see "*Gilead And AbbVie Are Not The Only Ones Re-Thinking CD47 Immunotherapies*" - Scrip, 28 Sep, 2023.)

Takeda announced the termination of TAK-994 development on 26 July after the orexin receptor 2 (OX2R) agonist was associated with hepatotoxicity in a Phase II study. TAK-994 was in development for narcolepsy type 1 (NT1).

Takeda presented the Phase II results as promising for the drug category despite the safety signal. “Although this study was not designed to compare TAK-994, the first-in-class oral OX2R agonist, with other narcolepsy drugs, its effectiveness on objective measures of wakefulness, self-reported assessment of daytime sleepiness, and frequency of cataplexy was impressive,” a principal investigator is quoted as saying in the press release.

The Phase II trial enrolled 73 patients randomized to three TAK-994 dose levels or placebo. Eight patients exceeded the liver enzyme level threshold, including three cases meeting Hy’s law criteria.

“No specific risk factors were identified,” Takeda said. “The current hypothesis is that TAK-994 associated drug-induced liver injury is caused by reactive metabolites and is unlikely to be an on-target effect of OX2R activation as orexin receptors are not expressed on human hepatocytes or on most immune cells.”

Another Takeda OX2R agonist is being studied in two Phase II trials for narcolepsy, the company said. That candidate, however, does not hold a BTD.

Strategic Decisions on RSV Vaccines

Respiratory syncytial virus protection was one of the regulatory success stories for the breakthrough program in 2023, but the large group helped to crowd out *Johnson & Johnson*'s RSV vaccine candidate.

Johnson & Johnson ended its 20,000+-patient Phase III EVERGREEN study of its RSV vaccine candidate while the trial was still enrolling, the company reported 29 March, citing imminent competition from the then-pending RSV vaccines from *Pfizer Inc.* and *GSK plc*. (Also see "*J&J Quits RSV Development With Two Rivals Already Poised For US Approval*" - Scrip, 29 Mar, 2023.)

J&J's RSV vaccine for older adults was about a year behind Pfizer's Abrysvo (approved 31 May for people 60 and older and 21 August for maternal immunization to protect infants) and GSK's Arexvy (approved 3 May for 60+ year olds).

RSV prophylaxis also notched wins for infants, thanks to Abrysvo's 21 August approval for maternal immunization and the 17 July approval of *AstraZeneca PLC*'s monoclonal antibody Beyfortus (nirsevimab-alip). Of the approvals, only Arexvy did not have a BTD.

J&J's decision to quit the field did not dissuade *Moderna, Inc.* from forging ahead with its RSV vaccine for older adults, which started a rolling BLA in mid-summer.

Efficacy Shortcomings

Another member of the RSV BTD group, Bavarian Nordic A/S's MVA-BN RSV, was discontinued in July after missing a primary efficacy endpoint.

Bavarian Nordic's 20,000+-patient Phase III VANIR trial enrolled more than 20,000 patients aged 60 and older. The vaccine fell short on a co-primary endpoint of efficacy in preventing at least three pre-defined symptoms of more severe disease. (Also see "*Bavarian Drops RSV Program After Phase III Flop*" - Scrip, 24 Jul, 2023.)

Efficacy shortfalls were more commonly a reason for complete response letters in 2023. The FDA has issued seven CRLs to products with BTDs this year, and every one touched on issues with efficacy evidence.

[*Editor's note: Keep track of CRLs with the Pink Sheet FDA Performance Tracker's Complete Response Letters chart*.]

The CRL announced on 9 August for *Galera Therapeutics, Inc.*'s avasopasem, a selective

dismutase mimetic seeking an indication for reduction in radiotherapy-induced severe oral mucositis in head and neck cancer patients, calls for an additional clinical trial.

Sage Therapeutics, Inc. and *Biogen, Inc.*'s neuroactive steroid Zursuvae (zuranolone) also requires an additional study or studies to support effectiveness in major depressive disorder. The companies sought indications for both MDD (with BTD) and a non-BTD claim for postpartum depression; only the PPD indication was approved on 4 August.

FDA requested additional data and analyses in a CRL for *F2G Ltd*'s orotomide antifungal olorofim announced on 19 June. The company plans to submit data from the now fully enrolled single-arm Phase IIb trial, which was included in the NDA with about the first half of its final patient count. The company is seeking a limited patient population of invasive fungal infection patients with limited or no treatment options.

The limited number of patients in the submitted trial was also cited in the FDA's CRL for *Eli Lilly and Company*'s Alzheimer's disease therapy donanemab. (Also see "*US FDA Rejects Lilly's Bid For Donanemab Accelerated Approval In Early Alzheimer's*" - Pink Sheet, 19 Jan, 2023.)

The CRL ended Lilly's bid for accelerated approval, but the company announced resubmission for full approval on 17 July with data from the confirmatory Phase III TRAILBLAZER-ALZ3 trial.

ImmunityBio's interleukin-15 (IL-15) superagonist complex N-803 received a CRL for BCG-unresponsive non-muscle invasive bladder cancer (NMIBC) carcinoma in situ that cites both clinical and quality issues, the company announced on 9 May. The FDA requested updated duration of response data and a safety update from the clinical trial as well as pointing to deficiencies identified in an inspection of third-party contract manufacturers.

Novo Nordisk A/S's tissue factor pathway inhibitor (TFPI)-targeting monoclonal antibody concizumab NDA for prophylaxis of bleeds in hemophilia A and B patients with inhibitors received an April CRL that called for additional information on dosing and monitoring of patients to ensure concizumab is administered properly. The CRL also sought more information on the manufacturing process.

No Next Act...

Most products that receive CRLs do go on to eventual approval, but some sponsors pull the plug after a letter. *Intercept Pharmaceuticals, Inc.*'s obeticholic acid for non-alcoholic steatohepatitis is the latest BTD product in this group, which also includes older discontinued candidates like *Y-mAbs Therapeutics Inc.*'s Omblastys (omburtamab), *Novartis AG*'s serelaxin, *Bayer AG*'s inhaled ciprofloxacin, *BioMarin Pharmaceutical Inc.*'s Kyndrisa (drisapersen) and *Clovis Oncology, Inc.*'s Xegafri (rociletinib).

Intercept announced the discontinuation of development of OCA for NASH on 22 June after receiving a CRL calling for long-term outcomes data from Phase III REGENERATE trial. An FDA advisory committee had concluded that the fibrosis reduction demonstrated in REGENERATE, while meeting statistical significance, was slight and did not overcome safety concerns.

Alfasigma S.p.A. announced an agreement to acquire Intercept on 26 September. (Also see "*Italy's Alfasigma Comes Calling After Intercept's Cruel Summer*" - Scrip, 26 Sep, 2023.)

...Unless There's A Next Act

Takeda decided to discontinue its breakthrough-designated budesonide oral suspension product TAK-721, previously known as Eohilia, in eosinophilic esophagitis instead of conducting the additional trial the FDA requested in a December 2021 CRL.

Then on 20 September 2023, Takeda announced that it had resubmitted the NDA for a revised indication limited to short term use. The company did not conduct another trial but reanalyzed the data and entered into dialog with the FDA. (Also see "*Keeping Track: Return & Renewal At US FDA*" - Pink Sheet, 23 Sep, 2023.)

In August, *Paradigm Biopharmaceuticals Ltd.* announced it was reviving SD-101, or Zorblisa, after acquiring the allantoin cream from *Amicus Therapeutics, Inc.*. SD-101 holds a BTD for treatment of epidermolysis bullosa.

Amicus had dropped SD-101 after a Phase III trial failed to meet its two co-primary endpoints and all secondary endpoints. (Also see "*Paradigm Plots Revival Of Butterfly Skin Drug After Amicus Deal*" - Scrip, 24 Aug, 2023.)