

# Anti-IL-5 biologics carve out severe-asthma niche



IL-5 inhibitors could help people with severe asthma whose airway inflammation is refractory to current treatments.

After posting positive results from two phase 3 clinical trials, London-based GlaxoSmithKline (GSK) stands poised to file with regulators all over the world for Bosatria (mepolizumab), a first-in-class drug targeting the proinflammatory cytokine interleukin-5 (IL-5). If approved, the humanized monoclonal antibody (mAb) could provide much needed therapeutic relief for a subgroup of people with asthma who are refractory to traditional inhalers and controller medications. Over the past decade, the asthma market has experienced very slow growth, with sales dominated by entrenched therapeutics such as short- and long-acting beta-agonists and inhaled corticosteroids. But with the realization that asthma is a heterogeneous disease, and that for some patients existing therapies are only relatively efficacious, the market for biologics tailored to different groups could grow. GSK's antibody is one of a clutch of IL-5 biologics vying to gain approval for severe asthma. Others are London-based AstraZeneca's benralizumab and Petach Tikva-based Teva Pharmaceutical's Cinquil (reslizumab).

IL-5 is a target for severe asthma because it regulates eosinophil maturation and survival. Eosinophils normally defend the body against helminthic parasites and other pathogens, but in some people with severe asthma, these white blood cells accumulate in the lungs and

promote airway inflammation after bronchial provocation by allergens. IL-5 inhibitors such as Bosatria and Cinquil stop the cytokine docking to the alpha chain of the IL-5 receptor complex on the surface of eosinophils and their precursor cells; benralizumab, by comparison, binds the receptor's alpha chain directly.

Not all severe asthma is driven by eosinophilic inflammation, but in those individuals where it is, IL-5 inhibition can be beneficial. In two phase 3 trials of Bosatria, the results of which were published September 25 in *The New England Journal of Medicine*, IL-5 blockers reduced airway hyper-responsiveness and improved various clinical endpoints. In one of the studies, led by researchers at GSK's Respiratory Therapeutic Area Unit in Research Triangle Park, North Carolina, 385 patients with severe eosinophilic asthma received intravenous or subcutaneous Bosatria, every four weeks. After 32 weeks, the treatment halved the exacerbation rates compared with the 191 patients in the placebo arm (0.93 and 0.81 exacerbations per patient per year in the intravenously and subcutaneously treated groups, compared with 1.75 in the placebo arm; *N. Engl. J. Med.* **371**, 1198–1207, 2014). "It's an incredibly large change to an incredibly meaningful endpoint," says coauthor Steven Yancey, GSK's medicine development leader for Bosatria.

The other phase 3 study of Bosatria included 135 people with severe asthma who needed daily glucocorticoid pills such as prednisone despite using high-dose inhaled therapies. At the end of the 24-week trial, individuals given Bosatria reduced their dose of oral glucocorticoids by a median of 50% compared with no reduction in the placebo group (*N. Engl. J. Med.* **371**, 1189–1197, 2014). "For patients with this type of eosinophilic asthma, I have not seen any drug in my career that is as effective as I saw this drug to be," says lead investigator Elisabeth Bel, head of respiratory medicine at the University of Amsterdam's Academic Medical Centre in the Netherlands.

Bosatria was well tolerated in both studies with a safety profile comparable to the placebo group. Ian Pavord, an asthma specialist at the University of Oxford, UK, and a coauthor on both phase 3 trial publications, points out, "Because it's a very selective inhibitor of eosinophilic airway inflammation, [Bosatria] doesn't come with the off-target effects that you get with oral steroids." GSK plans to file with the world's major drug regulatory bodies before the end of the year.

Analysts expect Bosatria will have a first-to-market advantage. But Teva's Cinquil might not

be far behind. In September, the Israeli company announced positive phase 3 trial results for the treatment of severe eosinophilic asthma. In top-line data from a 311-person study presented at the European Respiratory Society meeting in Munich, the company showed that monthly intravenous doses of Cinquil led to significant improvements in both pulmonary function and self-reported asthma control among patients with high eosinophil levels.

Meanwhile, MedImmune, a wholly-owned AstraZeneca subsidiary, is pursuing benralizumab for eosinophilic inflammation. Benralizumab targets an epitope on the alpha chain of the IL-5 receptor to prevent cytokine binding and ligand-induced signaling. This mechanism of action could result in more potent eosinophil depletion—and, thus, improved clinical outcomes—as there might be ligands other than IL-5 that also activate the receptor and trigger downstream inflammatory responses. In October, researchers published the results of a dose-ranging phase 2b study involving benralizumab that showed that the two higher doses reduced significantly asthma exacerbations in patients with raised eosinophil counts (*Lancet. Respir. Med.* doi:10.1016/S2213-2600(14)70201-2, 2014).

More than 300 million people globally have some form of asthma, although most patients can adequately manage the disease with existing therapies if taken appropriately. "All these monoclonals, in my opinion, are only required for those patients on the severest end of asthma," says Parameswaran Nair, a respirologist at McMaster University in Hamilton, Ontario, Canada. Those patients constitute between 5% and 10% of the total asthma population. And within this refractory group, around half have eosinophilic disease and would be eligible for IL-5–targeted therapies.

That's not a massive patient pool. And with cost pressures expected to keep the new mAbs priced at between \$10,000 and \$15,000 per patient per year, Matthew Scutcher, an analyst at Decision Resources in Burlington, Massachusetts, doesn't anticipate that any single new asthma biologic will become a blockbuster in what could become a crowded marketplace. "I don't think financially these drugs are going to be incredible," Scutcher says. "They will get paid for," he adds, noting that pharmacy benefit managers generally view the biologics as cost-effective in reducing hospitalizations and exacerbations, "but it will be late in the treatment algorithm."

By 2023, Scutcher predicts the total sales of all asthma biologics to top \$2.4 billion per year across the US, Japan and the five major

## Mouse mAb patent revoked

The European Patent Office (EPO) has revoked Tarrytown, New York–based Regeneron's patent on VelociMab, a mouse expression system for generating monoclonal antibodies, saying it lacked an inventive step as required by European patent law. Though the opposition procedure requested by European companies Kymab, Novo Nordisk and Merus renders the patent invalid, it remains in force as Regeneron has signaled its intention to appeal the decision to the EPO's Technical Board of Appeal.

## EMA adopts transparency policy

On October 2, the European Medicines Agency (EMA) adopted a new policy requiring drug companies to make public certain clinical data related to drug approvals. Starting on January 1, 2015, EMA will begin publishing trial data for companies that submit drugs for approval on or after that date. For medications already on the market that are approved for new indications, the rule takes effect next July. The agency hopes the new policy establishes increased confidence in the system and enables independent secondary analysis leading to public health benefits.

## Australia upholds *BRCA1* gene patent

The full bench of the Federal Court of Australia has decided unanimously in favor of Myriad Genetics, upholding its patent claim on the cancer-associated gene *BRCA1*. Though the patent had not been enforced by Myriad or its Australian licensor, Melbourne-based Genetic Technologies, *BRCA1* has been at the center of the worldwide debate on the legitimacy of gene patents. Attorneys for the plaintiff, cancer survivor Yvonne D'Arcy, indicated they plan to appeal the decision to Australia's High Court.

**“We've watched babies be rescued from what we thought would be great likelihood of death.”** Michael Whyte, a bone researcher at Shriners Hospitals for Children in St. Louis, on results of an open label phase 2 clinical trial that showed 89% of treated children survived to 5 years compared with 27% in historical control patients. Whyte led some of the studies on replacement enzyme asfotase alfa made by Alexion of Cheshire, Connecticut, in children with hypophosphatasia. (*Forbes*, 14 October 2014)

**“I cannot figure out how to search myself.”** Pittsburgh urologist Benjamin J. Davies tweeted about the CMS new Open Payments website that was launched September 30. According to the *New York Times*, the lead contractor for this government project was the same as for Healthcare.gov, CGI Federal, and we all know how that worked out. (*The New York Times*, 1 October 2014)

**Table 1** IL-5–targeted asthma therapies in clinical development

| Company              | Drug                   | Mechanism                                                                       | Delivery                     | Stage of development |
|----------------------|------------------------|---------------------------------------------------------------------------------|------------------------------|----------------------|
| GlaxoSmithKline      | Bosatria (mepolizumab) | Anti-IL-5 mAb                                                                   | Subcutaneous                 | Phase 3              |
| Teva Pharmaceutical  | Cinquil (reslizumab)   | Anti-IL-5 mAb                                                                   | Intravenous                  | Phase 3              |
| MedImmune            | Benralizumab           | Anti-IL-5 receptor alpha mAb                                                    | Subcutaneous                 | Phase 3              |
| MedImmune            | Talokinumab            | Anti-IL-13 mAb                                                                  | Subcutaneous                 | Phase 3              |
| Genentech            | Lebrikizumab           | Anti-IL-13 mAb                                                                  | Subcutaneous                 | Phase 3              |
| Regeneron and Sanofi | Dupilumab              | Anti-IL-4 receptor alpha mAb                                                    | Subcutaneous                 | Phase 2              |
| Pharmaxis            | ASM8                   | Antisense oligonucleotides targeting the IL-3, IL-5, GM-CSF and CCR3 receptors. | Inhalation                   | Phase 2              |
| Receptos             | RPC4046                | Anti-IL-13 mAb                                                                  | Intravenous and subcutaneous | Phase 1              |
| Novartis             | QBX258                 | Antibodies targeting IL-4 and IL-13                                             | Intravenous                  | Phase 2              |

EU markets. London-based Datamonitor Healthcare in an August 2014 report forecasted similar annual sales of \$2.7 billion by 2021 in these same seven countries. These estimates include sales of Xolair (omalizumab)—an anti-immunoglobulin E (IgE) antibody for treating allergic asthma that already pulls in over \$1 billion per year for its manufacturers, Genentech and Novartis. The sales figures also factor in several more anti-cytokine agents that are now in late-stage development. These include the phase 3 candidates talokinumab from MedImmune and lebrikizumab from Genentech, both of which target IL-13 to reduce airway inflammation, and Sanofi and Regeneron's phase 2 mAb dupilumab, which inhibits both IL-4 and IL-13. Dupilumab prevents the cytokines from interacting with the alpha subunit of the IL-4 receptor complex.

Which cytokines to block is a decision complicated by overlapping pathobiology. IL-5 is produced by T-helper-2 cells, and so are IL-4 and IL-13, and all play an important role in eosinophil accumulation. But these cytokines have other molecular functions that contribute to lung inflammation, too. For example, IL-4 and IL-13 are key mediators of IgE synthesis by B cells. They can also affect airway smooth muscle cell contractility and mucus production. These many culprit pathways implicated in airway inflammation means “it's going to be hard for clinicians and for payers to decide which of these therapies is right for which patient and when we should choose one over the other,” notes Michael Wechsler, director of the asthma program at National Jewish Health in Denver.

Researchers have been searching for reliable biomarkers that can discriminate between disease states and predict responsiveness to therapy with some success. Beyond using eosinophil counts to guide IL-5 treatment, clinicians have found that blood levels of periostin, a protein downstream of IL-4 and IL-13 signals, as well

as dipeptidyl peptidase 4, an enzyme activated by IL-13, are positively correlated with patient outcomes for experimental treatments targeted at those cytokines. What's more, IgE testing is already commonplace to determine the best candidates for Xolair to treat persistent allergic asthma.

These diagnostic biomarkers should point toward the primary trigger of asthma for individual patients. Yet, given that these various inflammatory drivers often occur together in the same individuals, tests might also indicate that some people require the simultaneous administration of more than one mAb. “Asthma is a multifactorial disease,” notes Amal Assaad, an allergist-immunologist at the Cincinnati Children's Hospital Medical Center in Ohio, “and most of these drugs are targeted against one mediator of asthma inflammation.”

One investigational drug that attempts to address the inherent complexity in asthma pathology comes from Pharmaxis. The Australian biotech's phase 2 candidate, ASM8, consists of two antisense oligonucleotides aimed at inhibiting the synthesis of receptor components involved in eosinophil activation and survival but also implicated in macrophage and mast cell signaling. One oligo targets the common beta chain of the IL-3, IL-5 and GM-CSF (granulocyte-macrophage colony-stimulating factor) receptors; the other hits the chemokine receptor CCR3. “They cover different nodes in the inflammation pathway,” says Wolfgang Jarolimek, head of drug discovery at Pharmaxis.

Anti-IL-5 therapies are also making a therapeutic mark in indications besides asthma. Both Bosatria and benralizumab are now in phase 3 trials for the treatment of eosinophilic COPD.

“People will be surprised by how widely applicable these treatments are,” says Pavord.

**Elie Dolgin** Somerville, Massachusetts