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Upstream Bio's Quest for Effective Best-in-Class Treatments for Allergic Inflammation

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From the β2-adrenoceptor agonists of the **early 1900s** to modern-day biologics, asthma treatment has come a long way in improving patients' lives. The past decade has marked major growth for the latter — a welcome advancement for those living with severe asthma.

Despite the progress, challenges remain in serving all patients with severe asthma. "While there are several steps of treatment going from mild to severe asthma, once you get to severe asthma, you're in a category of injectable biologics," stated Samantha Truex, CEO of Upstream Bio, a clinical-stage biotech company advancing new therapies to treat

inflammation. “Of all the patients who are eligible for a biologic, only about 20% of them get one.”

The majority of available therapies only treat the **most common type** of severe asthma (Type 2). Due to the lack of treatment options, people living with non-Type 2 asthma **often experience more** disease-related exacerbations and hospitalizations.

There has been a slow progression in this area. Several biologics have received FDA approval in recent years, which treat moderate-to-severe asthma. However, there is only one biologic not limited to one type of asthma currently approved by the FDA.

Samantha Truex
CEO of Upstream BIO

PURSUING UPSTREAM TARGETS WITH A BROADER REACH FOR SEVERE ASTHMA

Traditionally, asthma treatment is a one-size-fits-all approach, where therapies are often prescribed based on the patient's symptoms rather than the underlying mechanisms causing their asthma. Biologics targeting upstream factors for both Type 2 and non-Type 2 asthma inflammation pathways, like

thymic stromal lymphopoietin (TSLP), have emerged as the next generation of asthma treatment.

Patients with severe asthma may now benefit from treatments that address the root cause of their condition, irrespective of the specific type of asthma they have. “It's very helpful for a clinician and a patient to be able to rely on the potential for efficacy in a drug without even having to know the complexity of what asthma type that patient happens to suffer from,” said Truex.

A key driver in major allergic and inflammatory diseases like asthma, the TSLP signaling pathway has drawn the attention of industry drugmakers. TSLP lies upstream in the inflammatory cascade, ahead of immunoglobulin E and the interleukin receptors previously targeted by biologics. This positioning allows for treating both types of asthma and gets closer to the root of the disease before the influence of other disease-related cytokines.

Targeting TSLP may be a scalable approach across inflammatory conditions, said Truex. “One of the benefits of going after this upstream target is that it plays a role in allergic inflammation across many different diseases.” This is the rationale behind Upstream Bio’s lead clinical program, UPB-101.

UPB-101 BRINGS PROGRESS TO ASTHMA TREATMENT OPTIONS

Upstream Bio announced positive Phase 1b interim data in asthma patients for UPB-101 in a **press release** last month. Following its Phase 1b trial, Upstream is moving to Phase 2 with extended dosing intervals of 12 and 24 weeks — a break away from the traditional biweekly to monthly dosing regimen for injectable biologics.

UPB-101 is a recombinant fully human immunoglobulin G1 monoclonal antibody. While most assets targeting TSLP, including AstraZeneca's commercialized Tezspire, bind to the protein's ligand, UPB-101 targets the receptor with an aim to provide further differentiated treatment for these patients.

UPB-101 is the only inhibitor of TSLP biology to demonstrate sustained target engagement and maintained maximal inhibition of disease-related biomarkers in asthma patients 24 weeks after the last study dose. In the Phase 1b study of 32 asthmatic patients, UPB-101 resulted in a swift, substantial, and sustained reduction in disease-related biomarkers, including fractional exhaled nitric oxide (FeNO), and eosinophils through 32 weeks.

"We believe the potency of UPB-101 and its planned dosing interval of every 12 or 24 weeks with a single injection makes it a potential best-in-class therapeutic for severe inflammatory diseases," said Truex.

Based on the consistency of the preclinical and clinical data, UPB-101 has the potential to be the most potent TSLP inhibitor in the class, given that preclinical models have demonstrated that UPB-101 is at least four times more potent than Tezspire. The Phase 1b demonstrated that UPB-101 is highly potent with a Emax (maximal achievable effect) on FeNO of 43.4% reduction from baseline. For comparison, data published from the Tezspire program indicate an Emax of 27% FeNO reduction from baseline. Reduction in FeNO is known to be correlated with a reduction in asthma exacerbation rate, which the company reports, is the primary endpoint for Upstream Bio's asthma Phase 2 planned to start in Q1 2024.

"We believe UPB-101's potency indicates the potential for substantial efficacy across significantly extended dosing intervals that would relieve patients of frequent injections," Truex continued.

More TSLP-targeted potential therapies are in the clinical trial pipeline for severe asthma. But among the TSLP therapies in development, Upstream's anti-TSLPR UPB-101 is the only one with clinical data out to 32 weeks in asthmatic patients.

In June, Upstream Bio raised a **Series B private capital round** to support two global Phase 2 clinical trials for severe asthma and chronic rhinosinusitis with nasal polyps (CRSwNP), both planned to start by the first quarter of next year. They also announced the growth of their team to 30 people in total, leveraging notable clinical trial experience and

a partnership with an established global CRO partner.

The company has expanded its manufacturing capabilities to improve its drug yield and dose concentration in preparation for the upcoming trial. This manufacturing campaign aims to increase efficiency and scale and minimize doses to a single subcutaneous injection in future trials. Truex believes this has also set their program apart, “UPB-101 has a superior formulation relative to other inhibitors of TSLP biology. We believe it is the only agent in development studying Q24W administration with a single subcutaneous injection -- a major advantage to patients.”

The expansion into multiple diseases is propelled by shared biology and high rates of co-occurrence with severe asthma. CRSwNP is a chronic upper airway disease that is highly comorbid with asthma; up to **65% of patients** with CRSwNP also have asthma. TSLP receptor blocking could present one effective strategy for targeting chronic inflammatory conditions such as these.

Looking forward, sustained industry focus on upstream inflammatory targets could spell continued progress for people with asthma. Therapies that get closer to the root cause of inflammation and treat both types of severe asthma may open the doors for more patients to receive the necessary biologics to control their disease. The lead taken on by these patients in maintaining a frequent injection schedule remains, but advances

toward more potent interventions aim to relieve some of this burden.

"Though biologics have advanced therapy for patients with severe asthma very nicely and do serve some patients well, there's still quite a significant unmet need," said Truex. "And that need is driving continued innovation."

The insights team analyzes and comments on industry trends and creates thought leadership content for BioSpace and clients. The head of insights, Lori Ellis, can be contacted via **lori.ellis@biospace.com**. Follow her on ***LinkedIn***.

Related links

- **Upstream Bio Announces Positive Phase 1b Interim Data in Asthma and Company Progress Toward Phase 2**
- **Upstream Bio Adds Another $200M for Asthma, Allergy Pipeline**
- **Upstream Bio to Present New Clinical Data from Phase 1 Study of UPB-101 at the American Thoracic Society (ATS) International Conference**

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