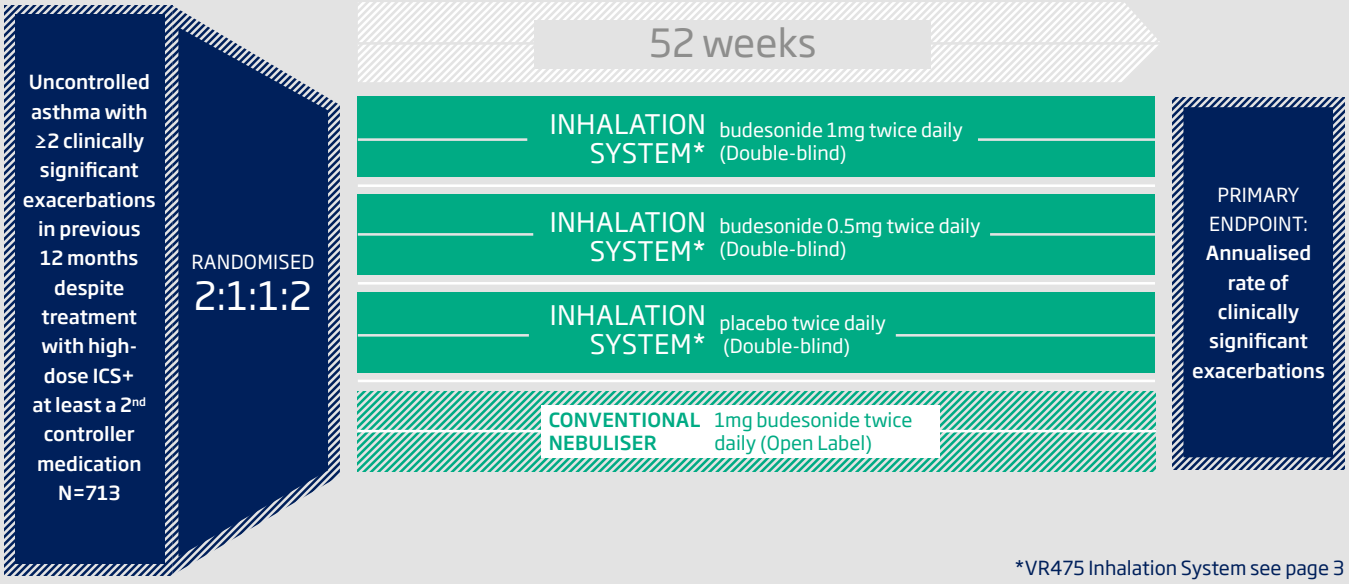
VR475 EUROPEAN DEVELOPMENT

VR475 is a wholly-owned drug-device combination product consisting of a budesonide inhalation suspension, with Vectura's novel proprietary VR475 Inhalation System. The VR475 Inhalation System is a breath-actuated jet nebuliser that guides the patient to inhale with a pre-set inspiratory flow rate and inhalation time per breath. Enabling optimal slow and deep inhalation by controlling the flow and volume of the patient's inhalation can ensure precise and targeted drug delivery to the patient's lungs. [1-4]

VR475 is currently in phase III development in patients with severe, uncontrolled asthma, and is being investigated as a potential therapy to reduce severe asthma attacks and improve asthma control. Headline results are expected in Q4 2018.

Phase III study overview

- Study recruitment complete, with headline data expected in Q4 2018.
- 713 severe asthma patients from 9 different countries.
- Double-blind, randomised, placebo controlled, parallel-group study to evaluate the efficacy and safety of two doses of VR475, with an open-label comparison to conventionally nebulised budesonide, in subjects with severe, uncontrolled asthma currently treated with a high dose inhaled corticosteroid (ICS) plus at least a second asthma controller.



*VR475 Inhalation System see page 3

Primary endpoint: Reduction in annualised rate of clinically significant exacerbations during the Treatment Period vs placebo.

Key secondary endpoints: Change from baseline in FEV1, in asthma control (by means of the Asthma-Control Questionnaire 5-items (ACQ-5)) and in reliever medication use vs placebo.

Four treatment groups: 1 mg, 0.5 mg budesonide suspension or placebo via the VR475 inhalation System (blinded) or 1 mg budesonide suspension via conventional jet nebuliser (open-label) with a 2:1:1:2 randomisation ratio and treated for up to 52 weeks.

Key Inclusion criteria: Adolescent (aged 12 to 17 years, inclusive) and adult (aged 18 to 74 years, inclusive) subjects with uncontrolled asthma despite treatment with high-dose ICS plus at least a second controller medication and a history of clinically significant exacerbations. Presence of uncontrolled asthma confirmed by spirometry (FEV1 < 80% of predicted normal value), evidence of reversible airflow limitation and an ACQ-5 score ≥1.5 points.

Phase IIb/III data

The phase III study is supported by the previously conducted positive phase IIb/III study in adults with oral corticosteroid (OCS) dependent asthma (study AICS-001), published in December 2014 [5] and summarised below.

Design
- Double-blind, randomised, placebo-controlled trial to evaluate tolerability, safety and efficacy of VR475 (nebulised budesonide suspension delivered by VR475 Inhalation system) in subjects with asthma requiring chronic oral corticosteroid treatment

Patients
- Severe asthma patients aged 18-65 years, requiring regular oral corticosteroids (GINA step 5)

Primary End Point
- OCS weaning over 18 weeks

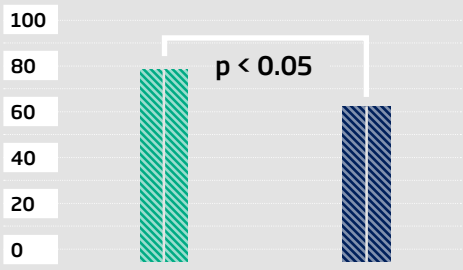
Study Sites
- 27 (Germany, Poland, Ukraine)

Treatments
- 1mg VR475 (n=80)
- Placebo delivered by VR475 inhalation system (n=40)
- 0.5mg VR475 (n=39)
- 1mg budesonide delivered by PARI LC Sprint jet nebuliser (open-label, n=40)

Primary Endpoint:

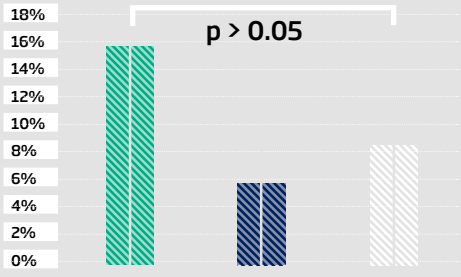
80.0% of VR475-treated patients reduced their OCS dose by ≥ 50% compared to 62.5% for placebo ($p < 0.05$)

% PATIENTS WITH OCS REDUCED BY ≥ 50%

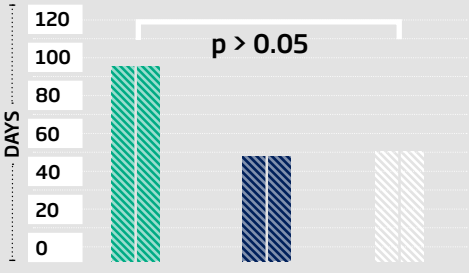


Key Secondary endpoints:

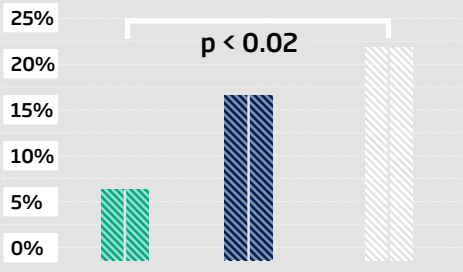
IMPROVEMENT IN FEV_1



TIME TO FIRST EXACERBATION (DAYS)



PATIENTS WITH ≥1 EXACERBATION



Footnote: Study AICS-001 was undertaken using Vectura's AKITA® breath-actuated jet nebuliser. VR475 will be commercialised using Vectura's FAVOLIR® breath-actuated jet nebuliser, a next-generation device with equivalent performance

Current asthma treatment guidelines

According to the Global Initiative for Asthma (GINA) guidelines [6] patients on Step 4 treatment (high dose ICS + long-acting beta agonist, LABA) with persistent symptoms or exacerbations, despite correct inhaler technique and good treatment adherence, have the following treatments options on Step 5:

1) Add-on tiotropium, in patients aged ≥12 years

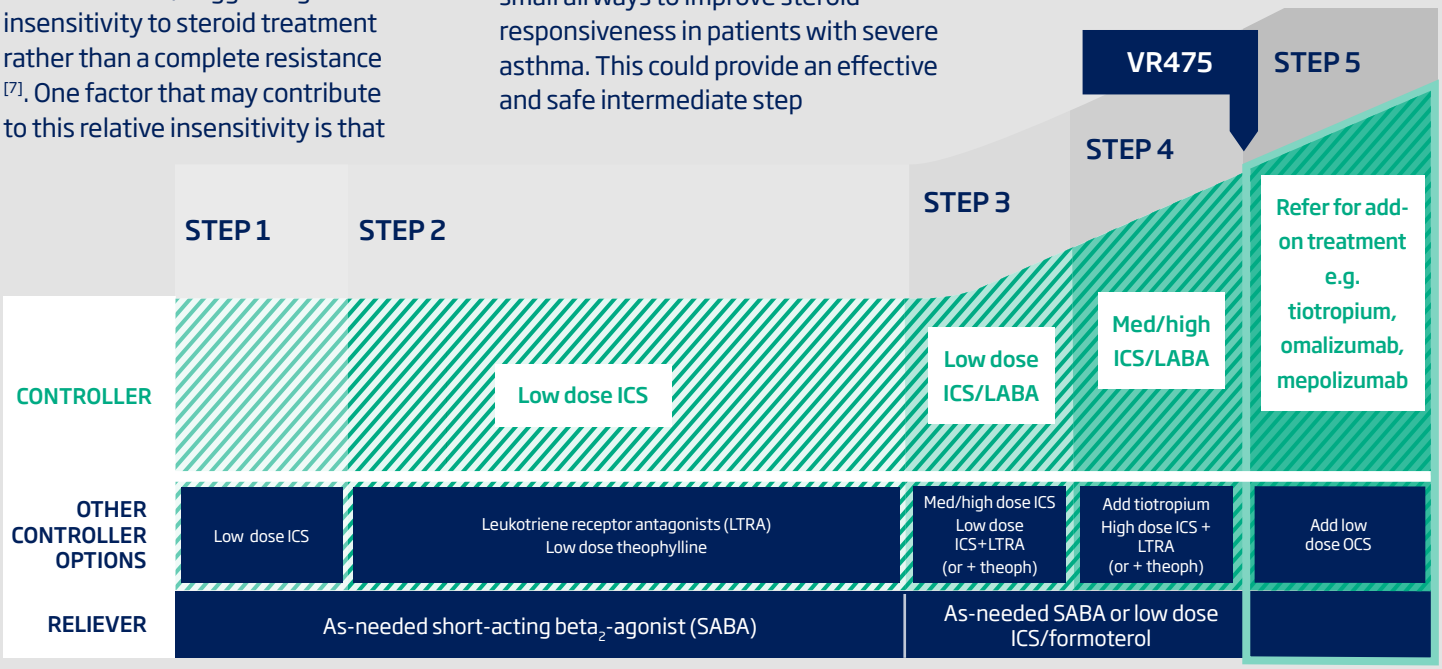
2) Add-on biologics:
- Anti-immunoglobulin E (anti-IgE) (omalizumab) treatment: for patients aged ≥6 years with allergic asthma
- Anti-interleukin-5 treatment (subcutaneous mepolizumab for patients aged ≥12 years; intravenous reslizumab for patients aged ≥18 years) or anti-interleukin-5 receptor treatment (subcutaneous benralizumab for patients aged ≥12 years), with eosinophilic asthma

3) Low dose oral corticosteroids (≤7.5 mg/day prednisone equivalent)

Potential new treatment option before biologics or oral corticosteroids (pre-GINA Step 5)

Patients who continue exhibiting airways inflammation despite high dose inhaled corticosteroids are often considered steroid-resistant. However, many such patients can improve asthma control and improve pulmonary function with oral or parenteral corticosteroids, suggesting relative insensitivity to steroid treatment rather than a complete resistance [7]. One factor that may contribute to this relative insensitivity is that inhaled formulations may not deliver enough drug to the small airways of the peripheral lung, where most of the asthma inflammation and physiological dysfunction occurs [8].

VR475 has the potential to increase delivery of budesonide to the small airways to improve steroid-responsiveness in patients with severe asthma. This could provide an effective and safe intermediate step between GINA Step 4 and GINA Step 5; the so-called GINA Step 4½, which would allow delaying or even avoiding GINA Step 5 therapies – very expensive biologics, and/or oral corticosteroids, which bring side effects that patients often find very difficult to deal with.



Source: http://ginasthma.org/

Nebulisation technology

A nebuliser administers medication in the form of a mist that is inhaled into the lungs. Nebulisers are particularly effective when a large dose of an inhaled medication is needed or when patients, such as infants, would have difficulty using an inhaler.

A patient's breathing pattern can alter the efficiency of drug delivery to different parts of the lung. Control of the inhalation flow rate, inhalation volume of the drug aerosol and the timing during inhalation when the aerosol is delivered can significantly affect how much drug gets to central or peripheral parts of the lungs. When using a conventional nebuliser, the normal "tidal" breathing pattern (short and shallow) leads to a lot of the delivered drug either being stuck at the back of the throat and swallowed, or mainly being delivered to the proximal part of the lungs, where anti-inflammatory drugs cannot maximise their action, as the inflammation often happens more distally [1, 4].

The smart technology in the VR475 Inhalation System optimises the amount of drug delivered to the lung by guiding the patient to inhale slowly and deeply during inhalation, ensuring the drug reaches the target site of action deeper into the lung. This breath-activated technology delivers the aerosol only during inhalation, so that no drug is wasted during exhalation time, as is the case with conventional jet nebulisers. The duration of each breath is adjustable to promote an ideal breathing pattern comfortable for the patient. This efficient drug administration allows for targeted drug deposition to the site of action, with the potential for greater efficacy.

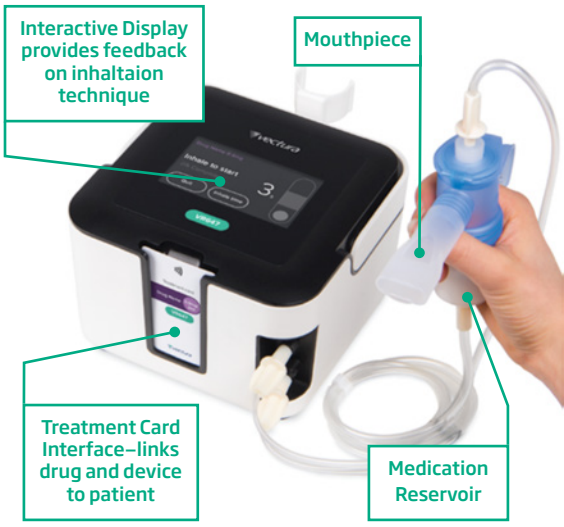


Image of Vectura's smart-technology breath-actuated jet nebuliser, FAVOLIR®, in development for VR475 Inhalation System commercialisation

Interactive patient feedback on inhalation technique, to provide reassurance that treatment has been administered correctly, also offers the potential to improve treatment adherence and hence clinical outcomes.

Study Risk

The key risk with the VR475/3/001 study is that it will fail to achieve a statistically significant reduction in clinically significant exacerbations in the VR475 arm compared to placebo. The indication studied in this clinical trial, where VR475 is provided as an add-on maintenance therapy for severe, uncontrolled asthma patients, is an unprecedented indication for nebulised budesonide, which is currently indicated for use in patients with bronchial asthma.

Indicative market size in Europe for severe asthma

- EU nebulised ICS market: $290m (IMS MIDAS Q3 2016 MAT)
- EU biologics market: $3bn by 2030 (Asthma & COPD. Forecast estimates from Decision resources Pharmacor Asthma (2016) COPD (2015) and select analyst reports)
- Peak sales potential: $150m - $300m (analyst consensus)
- In the EU 45% of all asthmatic patients are uncontrolled [9], and the severe uncontrolled asthmatics account for >50% of the asthma-related healthcare costs [10].

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