THERAPEUTIC ADVANCES in
Respiratory Disease

Plain Language Summary of Publication

Predicting response to benralizumab in patients with COPD: a plain language summary of publication of the GALATHEA and TERRANOVA studies

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Summary

What is this summary about?

- This is a plain language summary of two articles originally published in *The New England Journal of Medicine* and *The Lancet Respiratory Medicine*. These articles presented the results of GALATHEA and TERRANOVA, two clinical studies that took place across 41 countries.
  - GALATHEA and TERRANOVA measured how patients' COPD changed from before their first **benralizumab** (10, 30, or 100 mg) injection, to after 56 weeks of treatment.
  - In both studies, **benralizumab** was compared with **placebo**.
  - To see whether **benralizumab** treatment would benefit any particular patients included in these studies, researchers carried out an additional analysis following the main studies of GALATHEA and TERRANOVA.

How to say...

- **Benralizumab:** Ben–rah–LIZ–oo–mab
- **Eosinophil:** Ee–oh–SIN–oh–fill
- **Exacerbation:** Ig–za–ser–BAY–shun
- **Placebo:** Plah–SEE–bo
- **Bronchodilator:** Bron–co–DYE–late–or

Keywords: benralizumab, biologic, chronic obstructive pulmonary disease, eosinophil, GALATHEA, interleukin-5, TERRANOVA

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What were the main results of the GALATHEA and TERRANOVA studies?

- There was no meaningful difference in the average number of COPD **exacerbations** per year between **benralizumab** and **placebo**, among patients who had moderate to very severe COPD, blood **eosinophil** levels of ⩾220 cells per µl, and a history of COPD **exacerbations**.
- There were no safety concerns with **benralizumab**, similar to previous studies in patients with severe **eosinophilic** asthma treated with **benralizumab**.

What were the results of the additional analysis of GALATHEA and TERRANOVA?

- The additional analysis looked into whether there was a type of patient with moderate to very severe COPD who showed the most improvement (reductions in **exacerbations**) with the highest dose of **benralizumab** (100 mg). The analysis found that patients with the following combined characteristics before starting the studies received the most benefit from treatment with **benralizumab**:
  - Blood **eosinophil** levels of ⩾220 cells per µl, receiving triple inhaled therapy, and ⩾3 COPD **exacerbations** in the previous year.

What do the results of the additional analysis of GALATHEA and TERRANOVA mean?

- Patients with moderate to very severe COPD with a combination of the three identified characteristics above may be more likely to benefit from **benralizumab** 100 mg treatment. This needs to be investigated in further clinical studies.

Who should read this summary?

- This summary is intended for lay and non-specialist audiences, including patients with COPD and their family and caregivers, patient advocates, and healthcare professionals who do not specialize in COPD but may be involved in looking after patients with COPD.

Who sponsored these studies and this plain language summary?

- The GALATHEA and TERRANOVA studies, and this plain language summary, were all sponsored by AstraZeneca.

What is COPD?

- COPD is a long-term disease that causes inflammation and blocked airways, making it difficult for air to flow in and out of the lungs.
- In most cases, COPD is caused by breathing in substances that irritate the lungs (particularly cigarette smoke, pollutants, and fumes), these are called environmental risk factors. A person's genetic background can also contribute to the development of COPD.
- COPD has many different symptoms such as shortness of breath, a whistling sound when breathing (wheezing), tight chest, blocked airflow, extreme tiredness (fatigue), and cough. These symptoms can get worse over time, and make it harder to do regular activities, such as walking or climbing stairs.
- Patients with COPD often have other diseases as well, called "comorbidities."
    - Common comorbidities include cardiovascular disease (such as heart failure, coronary artery disease, and high blood pressure), lung cancer, anxiety, and depression.
- Patients with COPD often have **exacerbations**, or flare-ups. These are a worsening of symptoms that may lead to needing more medication or hospitalization.
    - **Exacerbations** can cause permanent damage to a patient's lungs and make their COPD worse, so preventing **exacerbations** is an important goal for treatment in COPD.
- COPD is a heterogeneous condition, meaning that different patients might have different symptoms, different types of inflammation, or even a different response to treatment.
- Some patients with COPD have more **eosinophils** in their blood than others.
    - **Eosinophils** are a type of white blood cell linked to inflammation.
    - High levels of **eosinophils** leads to inflammation in the airways, which may cause an **exacerbation** of COPD. Reducing **eosinophil** levels (such as with **benralizumab** treatment) has the potential to reduce **exacerbations** that are caused by this type of cell.
- For patients with COPD who have reduced airflow, COPD symptoms, and **exacerbations**, one treatment option is triple inhaled therapy.
    - Triple inhaled therapy is a combination of three medications (ICS, LABA, and LAMA) breathed in through the mouth or nose, to treat COPD.
    - Recent clinical study results have shown that people with COPD and high blood **eosinophil** levels who experience **exacerbations** despite triple inhaled therapy, might benefit from treatment with biologic medications.

What is benralizumab?

- **Benralizumab** is a biologic injection that quickly reduces the number of **eosinophils** in the blood, reducing associated inflammation and **exacerbations** of severe asthma
- **Benralizumab** can be prescribed by a doctor for people with severe asthma caused by high **eosinophil** levels who are aged 6 years or older in the United States or aged 18 years or older in the EU.
- In people with severe asthma caused by high **eosinophil** levels, **benralizumab** is injected under the skin and is given every 4 weeks for the first three injections; after this, it is given every 8 weeks.
- **Benralizumab** can also be used to treat people who have a rare disease called **eosinophilic** granulomatosis with polyangiitis (EGPA). People with EGPA have high levels of **eosinophils**, which causes inflammation of the blood vessels.
- **Benralizumab** can be prescribed by a doctor for adults with EGPA in the United States. In the EU, **benralizumab** can be prescribed as an "add-on" treatment for adults with EGPA whose disease keeps coming back after treatment or doesn't respond well to current treatment. In people with EGPA, **benralizumab** is injected under the skin and is given every 4 weeks.

Why were GALATHEA and TERRANOVA needed?

- Researchers wanted to know how safe and effective **benralizumab** might be in patients with moderate to very severe COPD, where triple inhaled therapy was not effective in preventing **exacerbations**.

How were the GALATHEA and TERRANOVA studies run to ensure findings were scientifically credible?

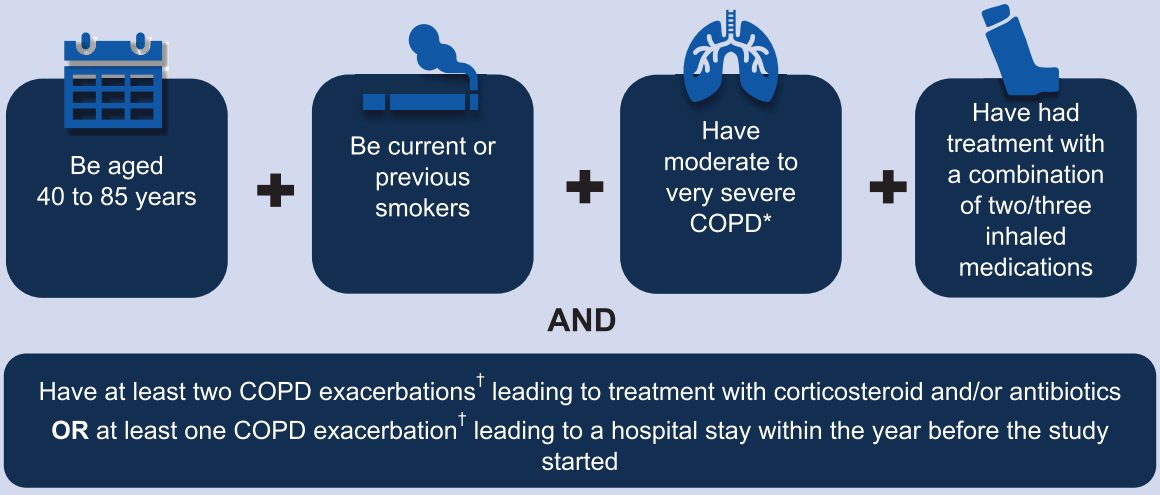
- Phase III: The researchers wanted to find out if **benralizumab** worked in a large number of patients with COPD; a phase III trial is a study where scientists look at how well a new treatment works and how safe it is when compared with receiving other treatment in a large population of patients. In most cases, a phase III trial is required so that a potential treatment can be approved.
- Randomized: Patients were assigned to study treatment by chance, to receive either **benralizumab** (at different doses) or **placebo**.
- Double-blind: None of the patients, researchers, study doctors, or other study staff knew who was given which **benralizumab** dose or **placebo**. This was done to make sure that the results were not influenced in any way while the study was in progress. When the study ended, the company that sponsored the clinical studies found out which treatments the patients were given so that they could analyze the results.
- **Placebo**-controlled: Researchers used a **placebo** to make sure that the effects they saw in the patients who were given **benralizumab** were caused by **benralizumab**, and not something else. The **placebo** looked like **benralizumab** but did not have any medicine in it.
- Parallel-group trial: Different groups of patients received different treatments; three groups received **benralizumab** at different doses and the other group received **placebo**.

Who took part in GALATHEA and TERRANOVA?

- The GALATHEA study included 1656 patients from 17 countries: Austria, Canada, Czech Republic, Germany, Hungary, Italy, Japan, Netherlands, Poland, Republic of Korea, Romania, Russian Federation, South Africa, Spain, Switzerland, United Kingdom, and the USA.
- The TERRANOVA study included 2254 patients from 26 countries: Argentina, Australia, Belgium, Brazil, Bulgaria, Chile, Colombia, Croatia, Denmark, France, Israel, Mexico, New Zealand, Norway, Peru, Philippines, Poland, Serbia, Slovenia, Sweden, Taiwan, Thailand, Turkey, Ukraine, the USA, and Vietnam.
- The GALATHEA and TERRANOVA studies had specific entry requirements for patients.

Entry requirements for the GALATHEA and TERRANOVA studies

To take part in GALATHEA and TERRANOVA, patients had to:

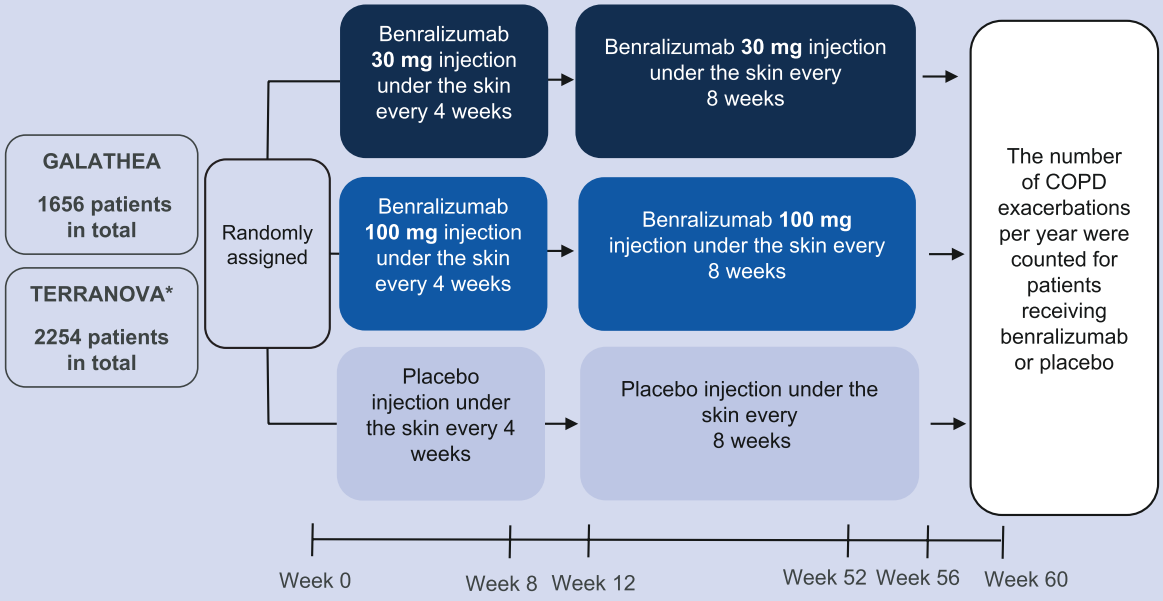


*Determined using post-bronchodilator FEV_1 (>20%–≤65% of the expected/normal FEV_1 value) and another measure of how well the lungs work called post-bronchodilator FEV_1/FVC (<0.70). Expected/normal FEV_1 values are based on average values from healthy people of the same age, gender, height, and race.
†A COPD exacerbation was defined as a worsening of COPD symptoms for at least 3 days resulting in corticosteroid and/or antibiotic treatment, hospitalization, or COPD-related death.

What did the GALATHEA and TERRANOVA studies evaluate?

- The studies assessed if **benralizumab** works for patients with moderate to very severe COPD, blood **eosinophil** levels of ⩾220 cells per µl, and a history of COPD **exacerbations**.
  - This was measured by the average number of COPD **exacerbations** patients had per year while receiving **benralizumab**.
  - The threshold of ⩾220 cells per µl was selected to ensure that patients who might have benefited from **benralizumab** treatment were able to participate in the study.
- The studies also wanted to assess how safe **benralizumab** is for patients with moderate to very severe COPD.
  - Throughout the studies, the patients' safety issues were recorded by the researchers. Safety issues that happen during studies are called adverse events. Researchers recorded the number and type of adverse events patients had during the study. The treatments used in the research may or may not have contributed to adverse events, but all are recorded so researchers can identify any unexpected patterns of safety issues. An adverse event is considered to be serious when it is life-threatening, causes long-term problems, or requires hospital care.
- Similar numbers of patients were randomly given **benralizumab** 30 mg, **benralizumab** 100 mg, or **placebo** for 56 weeks.

GALATHEA AND TERRANOVA study design



*TERRANOVA also included a group of patients who received 10 mg benralizumab every 4 weeks from Week 0–8, and every 8 weeks from Week 12–56 (not pictured), to assess the effect of different doses of benralizumab.

What were the characteristics of the patients who took part in GALATHEA and TERRANOVA?

- While the studies included patients with all levels of **eosinophils**, the main analysis focused on patients who had blood **eosinophil** levels of ⩾220 cells per µl because it was expected that this population of patients may benefit most from **benralizumab**.
- A total of 1120 patients from GALATHEA had blood **eosinophils** ⩾220 cells per µl. In these patients:
  - The average age was 66 years.
  - 71% were male.
  - 88% were White.
  - 66% were former smokers and 34% were current smokers.
  - All patients were using dual (ICS and LABA, or LABA and LAMA) or triple (ICS, LABA, and LAMA) inhaled therapy.
  - Patients had an average of two **exacerbations** in the past 12 months.
- A total of 1545 patients from TERRANOVA had blood **eosinophils** ⩾220 cells per µl. In these patients:
  - The average age was 65 years.
  - 66% were male.
  - 78% were White.
  - 71% were former smokers and 29% were current smokers.
  - All patients were using dual or triple therapy.
  - Patients had an average of two **exacerbations** in the past 12 months.

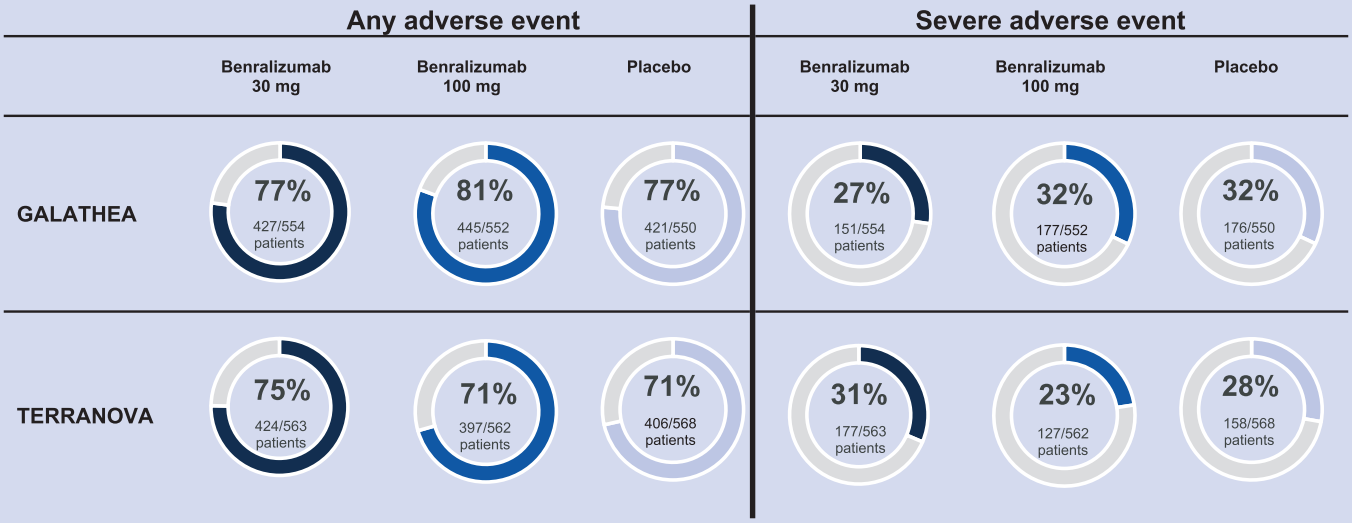
What was the main result of GALATHEA and TERRANOVA?

- In patients with moderate to very severe COPD who had blood **eosinophils** of ⩾220 cells per µl, and a history of **exacerbations**, **benralizumab** reduced the average number of COPD **exacerbations** per year compared with **placebo**. However, this level of reduction was not considered enough to be meaningful.

Were there any safety issues?

- The GALATHEA and TERRANOVA studies also looked at how safe **benralizumab** was.

The number of patients participating in GALATHEA and TERRANOVA who had adverse events



- During the entire 56 weeks of the study, the most common adverse events were nose and throat infections caused by viruses or bacteria, and infection of the main airways of the lungs (bronchitis).
- In both studies, the number of adverse events were similar between the **benralizumab** and **placebo** groups, and were consistent with results from other studies.

Why was an additional analysis performed?

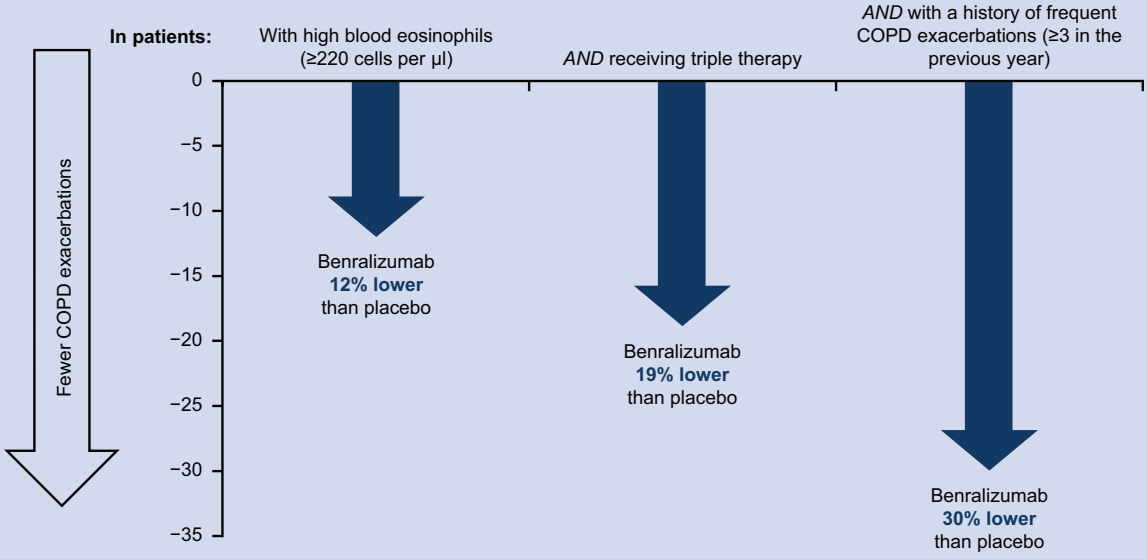
- The results from GALATHEA and TERRANOVA suggested that specific patient groups may respond differently to **benralizumab**.
- An additional analysis was carried out to see what specific traits and health features might indicate that a patient may benefit from **benralizumab** treatment.

What were the results of the additional analysis?

- *Please note, this Plain Language Summary only shows the combined results of patients from GALATHEA and TERRANOVA who were treated with **benralizumab** 100 mg or **placebo**.*
- Patients had a better response to **benralizumab** 100 mg if they had blood **eosinophil** levels of ⩾220 cells per µl, were receiving triple inhaled therapy, and had ⩾3 COPD **exacerbations** in the previous year.

Reductions versus placebo in the average number of COPD exacerbations per year for different patient characteristics when using benralizumab 100 mg every 8 weeks

All patients (100%; $n=2665$) had **eosinophil** levels of ⩾220 cells per µl; 19% ($n=515$) of these patients were also receiving triple inhaled therapy and had ⩾3 **exacerbations** in the past year.



What do the additional results of GALATHEA and TERRANOVA mean?

- The following combined characteristics resulted in the greatest reduction in the average number of **exacerbations** per year with **benralizumab** 100 mg compared with **placebo**:
  - **Eosinophil** levels of ⩾220 cells per µl,
  - Receiving triple inhaled therapy, and
  - ⩾3 COPD **exacerbations** in the past year
- Patients with all three of these characteristics may benefit from **benralizumab** 100 mg treatment, and this is being investigated in an ongoing study.

Where can I find the original articles on which this summary is based?

The original article "**Benralizumab** for the prevention of COPD **exacerbations**" was published in *The New England Journal of Medicine* in 2019 (Criner G.J. *et al. N Eng J Med.* 381, 1023–1034 [2019]). You can read the full article for free at: https://www.nejm.org/doi/full/10.1056/NEJMoa1905248.

The original article 'Predicting response to **benralizumab** in chronic obstructive pulmonary disease: analyses of GALATHEA and TERRANOVA studies' was published in *The Lancet Respiratory Medicine* in 2020 (Criner G.J. *et al. Lancet Respir Med.* 8, 158–170 [2020]). You can read the article at: https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(19)30338-8/fulltext.

Additional information on the GALATHEA and TERRANOVA studies is available at:

- GALATHEA study: NCT02138916 and 2013-004590-27.
- TERRANOVA study: NCT02155660 and 2013-004579-11.

Definitions:

- **Benralizumab:** A biologic injection that quickly reduces the number of **eosinophils** in the blood, reducing associated inflammation and severe asthma **exacerbations**.
- **Biologic:** A protein-based medication that targets specific cells or proteins in the body such as those involved in the immune system (the body's natural defense system) to reduce disease.
- **Bronchodilator:** A type of medication that opens the airways.
- **COPD (chronic obstructive pulmonary disease):** A long-term disease that causes inflammation and blocked airways, making it difficult for air to flow in and out of the lungs.
- **Eosinophil:** A type of white blood cell linked to inflammation.
- **Exacerbation:** A flare-up or worsening of symptoms that may lead to needing medication or hospitalization.
- **FEV_1 (forced expiratory volume in 1 second):** A test of how well the lungs are working, which measures the amount of air someone can forcefully breathe out in one second.
- **FVC (forced vital capacity):** A test of how well the lungs are working, which measures the total amount of air a patient can breathe out to empty their lungs.
- **Inflammation:** The body's response to injury or infection, which usually involves redness and swelling.
- **Microliter (µl):** A measure of volume for a liquid. One microliter is equal to a millionth of a liter.
- **Moderate to very severe COPD:** Determined using post-**bronchodilator** FEV_1 ($>20\%–\leqslant 65\%$ of the expected/normal value) and another measure of how well the lungs are working called post-**bronchodilator** FEV_1/FVC (<0.70).
- **Placebo:** An inactive treatment that looks like the medication being tested in a clinical study but does not have any medicine in it.
- **Post-bronchodilator:** After receiving a type of medication that opens the airways.
- **Triple inhaled therapy:** A combination of three medications breathed in through the mouth or nose, to treat COPD:
    - ICS (inhaled corticosteroid), LABA (long-acting β_2 agonist), and LAMA (long-acting muscarinic antagonist). ICS is a type of anti-inflammatory medication. LABA and LAMA are types of medication used to reduce COPD symptoms by relaxing the muscles lining the airways, which dilates (widens) the airways; this effect lasts for 12 h or more. LABA and LAMA work differently in the body and work better together than alone.

Declarations

Ethics approval and consent to participate

The trial designs were approved by the appropriate institutional review boards and independent ethics committees of the trial centers; all patients provided written informed consent.

Consent for publication

Not applicable.

Author contributions

Gerard J. Criner: Investigation; Writing – original draft; Writing – review & editing.

Dave Singh: Conceptualization; Writing – review & editing.

Alberto Papi: Investigation; Supervision; Writing – review & editing.

Maria Jison: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Supervision; Writing – review & editing.

Natalya Makulova: Conceptualization; Formal analysis; Investigation; Methodology; Writing – review & editing.

Vivian H. Shih: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Software; Supervision; Validation; Visualization; Writing – review & editing.

Laura Brooks: Formal analysis; Investigation; Methodology; Writing – review & editing.

Peter N. Barker: Formal analysis; Supervision; Writing – review & editing.

Ubaldo J. Martin: Conceptualization; Formal analysis; Methodology; Writing – review & editing.

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Competing interests

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Availability of data and materials

Data underlying the findings described in this manuscript can be requested in accordance with AstraZeneca's data-sharing policy described at https://astrazenecagroup-dt.pharmacm.com/DT/Home.

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