Biomarkers and clinical outcomes after cessation of tezepelumab after 2 years of treatment (DESTINATION)

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☐ I have no real or perceived conflicts of interest that relate to this presentation.
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<table>
<thead>
<tr>
<th>Affiliation / Financial interest</th>
<th>Commercial company</th>
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<tbody>
<tr>
<td>Grants and consultation fees:</td>
<td>4D Pharma, AstraZeneca, Chiesi, Genentech, GSK, Mologic, Novartis, Regeneron, Roche and Sanofi</td>
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Introduction to tezepelumab and the DESTINATION study

- **Tezepelumab** is a human monoclonal antibody that prevents thymic stromal lymphopoietin (TSLP) from interacting with its heterodimeric receptor\(^1,2\)

- **DESTINATION** was a phase 3, multicentre, randomized, placebo-controlled, double-blind, long-term extension study of patients (12–80 years old) who completed the phase 3 NAVIGATOR or SOURCE studies\(^2–4,a\)

- Long-term treatment with tezepelumab in **DESTINATION** resulted in fewer exacerbations, improvements in lung function and symptom control and reduced inflammatory biomarkers in patients with severe, uncontrolled asthma\(^4,b\)

- In a previous study, patients who stopped biologic treatment showed increased blood eosinophils and exacerbations, and decreased asthma control and lung function compared with those who continued\(^5\)

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\(^a\)Only patients from the NAVIGATOR parent study were eligible for a 36-week extended follow-up. \(^b\)The protocol was amended in light of the COVID-19 pandemic. Patients aiming to enrol in the DESTINATION study who were not able to attend an on-site EOT visit in either parent study continued to participate in the 12-week safety follow-up period of either NAVIGATOR or SOURCE until on-site randomization and administration of the first dose of study treatment in DESTINATION could be conducted. Figure adapted from Menzies-Gow A et al. Respir Res 2020;21:266 (under a CC BY 4.0 licence (http://creativecommons.org/licences/by/4.0/) and Brusselle GG et al. N Engl J Med 2022;386:157–71. COVID-19, coronavirus disease 2019; EOT, end of treatment

Patients included in this analysis received tezepelumab in both NAVIGATOR and DESTINATION (tezepelumab group) or placebo in both NAVIGATOR and DESTINATION (placebo group). Patients who received placebo in NAVIGATOR and were re-randomized to tezepelumab in DESTINATION were not included in this analysis. *Patients were also required to have attended the EOT visit at the end of DESTINATION, although those who could not attend the last visit owing to COVID-19 could still participate in this analysis.

EFU, extended follow-up; EOT, end of treatment; LTE, long-term extension; Q4W, every 4 weeks; R, randomization; SC, subcutaneously
To explore the effects of tezepelumab cessation after 2 years of treatment (210 mg Q4W)

Change over time was assessed in:

- Blood eosinophil count
- FeNO level
- ACQ-6 score
- Pre-BD FEV₁
Baseline demographics and clinical characteristics of patients (at the start of NAVIGATOR) who entered the extended follow-up period

<table>
<thead>
<tr>
<th>Baseline demographic/characteristic</th>
<th>Tezepelumab (n = 289)</th>
<th>Placebo (n = 137)</th>
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<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>48.5 (17.3)</td>
<td>47.1 (17.8)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>180 (62.3)</td>
<td>81 (59.1)</td>
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<tr>
<td>Body mass index, kg/m², mean (SD)</td>
<td>28.9 (7.0)</td>
<td>28.4 (7.5)</td>
</tr>
<tr>
<td>ICS dose group, n (%)</td>
<td></td>
<td></td>
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<tr>
<td>Medium</td>
<td>57 (19.7)</td>
<td>33 (24.1)</td>
</tr>
<tr>
<td>High</td>
<td>232 (80.3)</td>
<td>103 (75.2)</td>
</tr>
<tr>
<td>Maintenance oral corticosteroid use, n (%)</td>
<td>19 (6.6)</td>
<td>6 (4.4)</td>
</tr>
<tr>
<td>Number of exacerbations in the past 12 months from NAVIGATOR, n (%)</td>
<td></td>
<td></td>
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<tr>
<td>≤ 2</td>
<td>179 (61.9)</td>
<td>90 (65.7)</td>
</tr>
<tr>
<td>&gt; 2</td>
<td>110 (38.1)</td>
<td>47 (34.3)</td>
</tr>
<tr>
<td>Blood eosinophil count, cells/µL, median (min, max)</td>
<td>270 (0, 1340)</td>
<td>260 (10, 980)</td>
</tr>
<tr>
<td>FeNO levels, ppb, median (min, max)</td>
<td>31.0 (5.0, 213.0)</td>
<td>27.0 (5.0, 258.0)</td>
</tr>
<tr>
<td>Serum total IgE, IU/mL, median (min, max)</td>
<td>250.0 (1.5, 12 823.2)</td>
<td>226.8 (1.5, 7632.3)</td>
</tr>
<tr>
<td>FEIA-positive for any perennial aeroallergen, n (%)</td>
<td>194 (67.1)</td>
<td>93 (67.9)</td>
</tr>
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</table>

Patients included in this analysis received tezepelumab in both NAVIGATOR and DESTINATION (tezepelumab group) or placebo in both NAVIGATOR and DESTINATION (placebo group). Medium-dose ICS: fluticasone propionate 500 µg/day or equivalent; high-dose ICS: fluticasone propionate > 500 µg/day or equivalent; one patient in the placebo group received fluticasone propionate < 500 µg/day or equivalent.

FEIA, fluorescence enzyme immunoassay; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroids; IgE, immunoglobulin E; Q4W, every 4 weeks; SD, standard deviation.
BECs gradually increased from week 4 after the last dose of tezepelumab

Panels A and B show fold change in adjusted means and 95% CIs from the start of NAVIGATOR (week 0) through to last dose (week 10) and over the 40-week period after last dose. Log-transformed ratio change (actual value/baseline) was modelled using treatment group, region, age, log baseline BEC, visit and treatment-by-visit as covariates. Fold change from baseline is the geometric mean of the ratio (actual value/baseline), where a fold change of 1 is no change from baseline, a 0.5 fold change corresponds to halving from baseline. Pretreatment baseline was defined as the last non-missing measurement recorded before randomization in NAVIGATOR. Tezepelumab group: patients who received tezepelumab in NAVIGATOR and DESTINATION; placebo group: patients who received placebo in NAVIGATOR and DESTINATION. BEC, blood eosinophil count; CI, confidence interval; LTE, long-term extension

A) Fold change over time in BEC from the start of the NAVIGATOR study

B) Fold change over time in BEC from tezepelumab cessation
FeNO levels gradually increased from week 4 after the last dose of tezepelumab

A) Fold change over time in FeNO levels from the start of the NAVIGATOR study

B) Fold change over time in FeNO levels from tezepelumab cessation

Panels A and B show fold change in adjusted means and 95% CIs from the start of NAVIGATOR (week 0) through to last dose (week 100) and over the 40-week period after last dose. Log-transformed ratio change (actual value/baseline) was modelled using treatment group, region, age, log baseline FeNO level, visit and treatment-by-visit as covariates. Fold change from baseline is the geometric mean of the ratio (actual value/baseline), whereby a fold change of 1 is no change from baseline, a 0.5 fold change corresponds to halving from baseline. Pre-treatment baseline was defined as the last non-missing measurement recorded before randomization in NAVIGATOR. Tezepelumab group: patients who received tezepelumab in NAVIGATOR and DESTINATION; placebo group: patients who received placebo in NAVIGATOR and DESTINATION. CI, confidence interval; FeNO, fractional exhaled nitric oxide; LTE, long-term extension
Pre-BD FEV\textsubscript{1} gradually decreased from week 4 after the last dose of tezepelumab.

A) Change over time in pre-BD FEV\textsubscript{1} from the start of the NAVIGATOR study

B) Change over time in pre-BD FEV\textsubscript{1} from tezepelumab cessation

Panels A and B show adjusted means and 95% CIs from the start of NAVIGATOR (week 0) through to last dose (week 100) and over the 40-week period after last dose. Mean changes after cessation of tezepelumab from baseline at each week for pre-BD FEV\textsubscript{1} were estimated using a repeated measures model with treatment group, region, age, baseline pre-BD FEV\textsubscript{1}, visit and treatment-by-visit as covariates. Estimates are least-squares means. Pre-treatment baseline was defined as the last non-missing measurement recorded before randomization in NAVIGATOR. Tezepelumab group: patients who received tezepelumab in NAVIGATOR and DESTINATION; placebo group: patients who received placebo in NAVIGATOR and DESTINATION. BD, bronchodilator; FEV\textsubscript{1}, forced expiratory volume in 1 second; LTE, long-term extension.
ACQ-6 scores gradually increased from week 4 after the last dose of tezepelumab

Panels A and B show adjusted means and 95% CIs from the start of NAVIGATOR (week 0) through to last dose (week 100) and over the 40-week period after last dose. Mean changes after cessation of tezepelumab from baseline at each week for ACQ-6 were estimated using a repeated measures model with treatment group, region, age, baseline ACQ-6 score, visit and treatment-by-visit as covariates. Estimates are least-squares means. Pre-treatment baseline was defined as the last non-missing measurement recorded before randomization in NAVIGATOR. Tezepelumab group: patients who received tezepelumab in NAVIGATOR and DESTINATION; placebo group: patients who received placebo in NAVIGATOR and DESTINATION. ACQ-6, Asthma Control Questionnaire-6; LTE, long-term extension.
The effects of tezepelumab treatment, namely biomarker suppression and improved clinical outcomes, gradually waned in the 40 weeks after cessation of tezepelumab treatment, but did not return to baseline.

The effects of tezepelumab cessation on the reductions in serum total IgE levels achieved during NAVIGATOR and DESTINATION are also presented at ERS 2023 (OA1419).

Further study to explore which patient subgroups may achieve sustained asthma control is required to assess the potential disease-modifying effect of tezepelumab.