Efficacy of Dupilumab versus Tezepelumab in Asthma Patients: Matching-Adjusted Indirect Comparison of Long-Term Extension Trials

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DUPILUMAB

Background

- Dupilumab and tezepelumab, biologic therapies for asthma, were approved in the United States in 2018 and 2021, respectively.[1,2] To date, there have been no head-to-head trials between the two biologics.
- The long-term relative efficacy of the two biologics can be estimated through indirect treatment comparison (ITC) studies after matching baseline patient characteristics from the available long-term extension (LTE) trials.[3]
- While the dupilumab asthma trial (LIBERTY ASTHMA QUEST) included a broader patient population (≥1 exacerbation at baseline),[4] the tezepelumab trial (NAVIGATOR) included patients with 2 or more severe exacerbations in the prior year, with ~40% having >3 exacerbations.[5]

Objective

- **To estimate the long-term relative efficacy of dupilumab (300 mg every 2 weeks; up to 3 years) versus tezepelumab (210 mg every 4 weeks; up to 2 years) in adolescents and adults with asthma using an unanchored matching-adjusted indirect comparison (MAIC).**

Conclusions

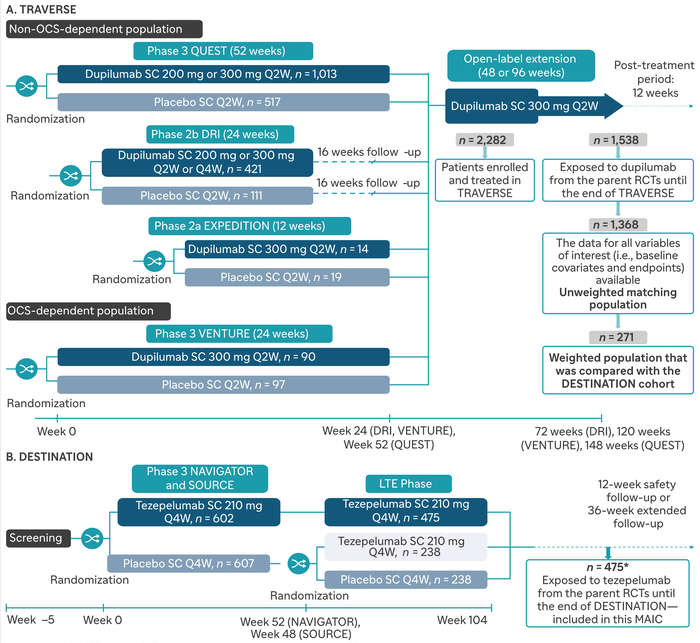
- **In this MAIC, long-term dupilumab treatment appeared to demonstrate a lower annualized exacerbation rate for all asthma exacerbations and a greater lung function improvement than tezepelumab in the matched cohorts. No difference was observed in AERs leading to a hospitalization and/or an ER visit.**
- **Limitations of this ITC include the inability to match patients' data at LTE entry due to data unavailability, and potential unmeasured confounding variables.**
- **Additional data from head-to-head trials or observational studies comparing both treatments would be valuable in making informed treatment decisions.**

Methods and Results

Data source

- A literature search was conducted that identified two LTE trials, TRAVERSE[6] (NCT02134028) and DESTINATION[7] (NCT03706079), which investigated the long-term efficacy of dupilumab and tezepelumab, respectively, in patients with asthma (**Figure 1**).
- Owing to the absence of a common comparator arm in the TRAVERSE and DESTINATION trials, an unanchored MAIC was employed as per the NICE-DSU 18 guideline.[3]

Figure 1. Study design of TRAVERSE and DESTINATION: Patients receiving dupilumab or tezepelumab from the baseline of parent RCTs until the end of TRAVERSE/DESTINATION were considered for the MAIC.



Note: In the TRAVERSE trial, the OLE treatment duration was initially planned for 96 weeks. However, accumulating safety data for dupilumab across multiple indications led to a protocol amendment, i.e., reducing the OLE treatment duration to 48 weeks. The majority of patients in the TRAVERSE trial underwent follow-up between 72 and 148 weeks, with one patient being followed up for 157 weeks. The total treatment duration, including parent studies, of the DESTINATION trial was 104 weeks. *This includes 415 patients from the NAVIGATOR trial and 60 patients from the SOURCE trial, who received tezepelumab from the baseline of the parent RCTs until the end of DESTINATION.
LTE, long-term extension; OCS, oral corticosteroid; MAIC, matching-adjusted indirect comparison; OLE, open-label extension; Q2W, every 2 weeks; Q4W, every 4 weeks; RCT, randomized controlled trial; SC, subcutaneous.

Matching-adjusted Indirect comparison

- Individual patient data of dupilumab from the TRAVERSE trial and the parent randomized controlled trials (RCTs) were reweighted to match the aggregate tezepelumab data from the DESTINATION trial and the parent RCTs for prognostic factors and treatment effect modifiers (validated based on clinicians' input, **Table 1**).
- A sensitivity analysis (SA) further matched patients in TRAVERSE and DESTINATION based on key covariates (blood eosinophil, fractional exhaled nitric oxide, and the number of exacerbations in the prior year), as suggested by clinicians in the context of moderate-to-severe asthma, which might have significantly impacted the efficacy outcomes.
- Outcomes included (from the baseline of parent RCTs to end of TRAVERSE or DESTINATION):
  - Annualized exacerbation rate (AER) of all asthma exacerbations
  - AER of asthma exacerbations leading to a hospitalization and/or an emergency room (ER) visit
  - Change from baseline in pre-bronchodilator forced expiratory volume in 1 s (pre-BD FEV_1, L)

Matching of baseline covariates

- Before matching, the DESTINATION trial had 94.7% of patients with ≥2 exacerbations because the NAVIGATOR trial included patients with ≥2 exacerbations, with ~40% having at least 3 exacerbations in the previous 12 months.[5] Additionally, patients in the DESTINATION trial reported higher use of OCS compared to those in the TRAVERSE trial. In the primary analysis, the baseline covariates were matched for all prognostic factors and treatment effect modifiers between the two treatments (**Table 1**).

Table 1. Baseline demographic and clinical characteristics of patients in the TRAVERSE and DESTINATION trials before and after matching – primary analysis

Covariates	Unweighted TRAVERSE (*N* = 1,368)	Weighted TRAVERSE (ESS, *N* = 271)	DESTINATION (*N* = 475)
Age, mean ± SD (years)	48.76 ± 14.34	50.12 ± 16.00	50.12 ± 16.00
Male (%)	39.8	36.6	36.6
BMI, mean ± SD (kg/m^2)	28.94 ± 6.32	29.11 ± 7.14	29.11 ± 7.14
Eosinophil count, mean ± SD (giga/L)*	0.36 ± 0.41	0.31 ± 0.29	0.31 ± 0.29
FeNO, mean ± SD (ppb)*	35.87 ± 33.09	39.76 ± 35.33	39.76 ± 35.33
FEV_1, mean ± SD (L)	1.78 ± 0.60	1.80 ± 0.68	1.80 ± 0.68
Percentage predicted FEV_1, mean ± SD (%)	58.40 ± 13.31	61.74 ± 17.39	61.74 ± 17.39
IgE, mean ± SD (IU/mL)	449.96 ± 788.07	479.47 ± 918.08	479.47 ± 918.08
Allergic rhinitis (ongoing) (%)	65.6	59.8	59.8
One exacerbation in the year prior to the parent RCT (%)*	49.8	5.3	5.3
Two exacerbations in the year prior to the parent RCT (%)*	25.4	58.3	58.3
>2 exacerbations in the year prior to the parent RCT (%)*	23.6	36.4	36.4
ICS users (%)	99.3	100.0	100.0
OCS users (%)	5.8	18.7	18.7

In the primary analysis, the post-matching ESS for the dupilumab cohort was 271, i.e., 19.8% of the original TRAVERSE sample.
In the sensitivity analysis, the ESS for the TRAVERSE trial, after matching selected key covariates was 680.
*Sensitivity analysis included these covariates as suggested by clinicians in the context of moderate-to-severe asthma.
BMI, body mass index; ESS, effective sample size; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 s; ICS, inhaled corticosteroid; IgE, immunoglobulin E; IU, international unit; OCS, oral corticosteroid; ppb, parts per billion; RCT, randomized controlled trial; SD, standard deviation.

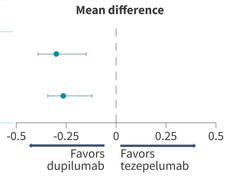
Outcomes in matched patient cohorts

- Dupilumab demonstrated a significantly lower AER for all asthma exacerbations than tezepelumab (mean difference [MD]: –0.269; $p < 0.0001$), with similar results in the SA (**Figure 2A**).
- A comparable reduction was observed in AERs leading to a hospitalization and/or an ER visit between the two treatments (MD: 0.006; $p = 0.62$) in both primary analysis and SA (**Figure 2B**).
- The change from baseline in pre-BD FEV_1 (L) was numerically higher with dupilumab than with tezepelumab in the primary analysis (MD: -0.064; $p = 0.07$). However, the SA demonstrated a significantly greater improvement with dupilumab than with tezepelumab (MD: -0.153; $p < 0.0001$) (**Figure 2C**).

Figure 2. MAIC results in matched patients receiving dupilumab and tezepelumab

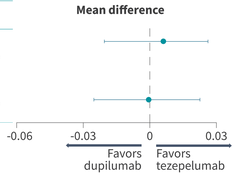
A. AER of all asthma exacerbations[a]

	Mean AER from TRAVERSE	Mean AER from DESTINATION	MD (95% CI), *p*-value
Weighted TRAVERSE vs. DESTINATION (primary analysis)	0.471	0.740	-0.269 (-0.372; -0.166), $p < 0.0001$
Weighted TRAVERSE vs. DESTINATION (sensitivity analysis)	0.493	0.740	-0.247 (-0.349; -0.146), $p < 0.0001$



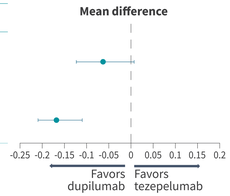
B. AER of asthma exacerbations leading to a hospitalization and/or an ER visit[a]

	Mean AER from TRAVERSE	Mean AER from DESTINATION	MD (95% CI), *p*-value
Weighted TRAVERSE vs. DESTINATION (primary analysis)	0.048	0.043	0.006 (-0.016; 0.027), $p = 0.62$
Weighted TRAVERSE vs. DESTINATION (sensitivity analysis)	0.042	0.043	-0.0003 (-0.022; 0.021), $p = 0.98$



C. Change from baseline in pre-BD FEV_1 (L)[b]

	Mean CFB from DESTINATION	Mean CFB from TRAVERSE	MD (95% CI), *p*-value
DESTINATION vs. Weighted TRAVERSE population (Primary analysis)	0.204	0.268	-0.064 (-0.132; 0.005), $p = 0.07$
DESTINATION vs. Weighted TRAVERSE population (Sensitivity analysis)	0.204	0.357	-0.153 (-0.207; -0.099) $p < 0.0001$



Note: The majority of patients in the TRAVERSE trial underwent follow-up between 72 and 148 weeks from the baseline of the parent RCTs, with one patient being followed up for 157 weeks. [a]Estimated from the baseline of the parent RCTs to the end of TRAVERSE (i.e., 72 to 157 weeks) or DESTINATION (104 weeks). For TRAVERSE, this duration included 72-week data for P2b and VENTURE trial patients and 148-week data for QUEST trial patients. One patient was followed up for up to 157 weeks. [b]Estimated from the baseline of the parent RCTs to 72 to 100 weeks of TRAVERSE and 104 weeks of DESTINATION. For TRAVERSE, this duration included 72-week data for P2b and VENTURE trial patients and 100-week data for QUEST trial patients. For unweighted TRAVERSE and DESTINATION patients, the mean AERs were 0.446 and 0.740 in the primary analysis and 0.493 and 0.740 in the sensitivity analysis, respectively; the mean AERs leading to a hospitalization and/or ER visit were 0.034 and 0.043, respectively, in both the primary and sensitivity analyses; the mean change from baseline in pre-BD FEV_1 (L) were 0.339 and 0.204 in the primary analysis and 0.338 and 0.204 in the sensitivity analysis, respectively. AER, annualized exacerbation rate; CFB, change from baseline; CI, confidence interval; ER, emergency room; MAIC, matching-adjusted indirect comparison; MD, mean difference; pre-BD FEV_1, pre-bronchodilator forced expiratory volume in 1 s; RCT, randomized controlled trial.

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CONFLICTS OF INTEREST
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SA is an employee of RTI Health Solutions and a paid consultant at Sanofi.
W-HC is a former Sanofi employee.

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