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Non-typeable *Haemophilus influenzae-Moraxella catarrhalis* vaccine for the prevention of exacerbations in COPD: a multicentre, randomised, controlled, observer-blinded phase 2b trial

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Zusammenfassung des wissenschaftlichen Inhalts

Stefan Andreas

Exazerbationen der chronisch obstruktiven Lungenerkrankung (COPD) sind eine der Hauptursachen für Krankenhauseinweisungen und Tod. Bisher gibt es nur wenige Maßnahmen, um diese Exazerbationen zu reduzieren. Es werden dringend neue therapeutische Ansätze benötigt.

Eine bakterielle Besiedlung der Atemwege spielt in der Pathogenese von Exazerbationen eine wesentliche Rolle, weshalb ein Impfstoff, der auf Bakterien in den Atemwegen abzielt, Exazerbationen verhindern könnte. Dieser Ansatz wurde erstmalig in einer großen randomisierten und kontrollierten Studie mit einem Impfstoff gegen nicht typisierbaren Haemophilus influenzae (NTHi) und Moraxella catarrhalis (Mcat) mit dem Endpunkt Exazerbationen bei Patienten mit COPD untersucht.

Der primäre Endpunkt, die Rate der mittelschweren oder schweren Exazerbationen, zeigte keinen Unterschied zwischen der Impfstoff- und der Placebogruppe. In den definierten Untergruppenanalysen zeigte sich jedoch, dass die Rate schwerer Exazerbationen und damit verbundener Krankenhausaufenthalte mit dem Impfstoff reduziert wurde. Der Impfstoff bewirkte weiter eine anhaltende spezifische Immunreaktion gegen NTHi und eine geringere Immunreaktion gegen Mcat. Die T-Zell-Antworten waren variabler. In der Placebogruppe traten 10 Todesfälle auf; in der Verumgruppe ein Todesfall.

Auch wenn der primäre Endpunkt negativ ist, wird in einem begleitenden Editorial diskutiert, dass der neue Ansatz in der Prävention schwerer, bakteriell vermittelter Exazerbationen wirksam sein könnte. Weitere Studien zu den Effekten des Impfstoffes bei unterschiedlichen Exazerbationsphänotypen seien nun erforderlich. Die aktuelle Pandemie hat gezeigt, dass eine große Zahl von Patienten für Impfstudien erfolgreich rekrutiert werden kann.

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Non-typeable *Haemophilus influenzae–Moraxella catarrhalis* vaccine for the prevention of exacerbations in chronic obstructive pulmonary disease: a multicentre, randomised, placebo-controlled, observer-blinded, proof-of-concept, phase 2b trial

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Summary

Background Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are associated with changes in the sputum microbiome, including an increased prevalence of pathogenic bacteria. Vaccination against the most frequent bacteria identified in AECOPD might reduce exacerbation frequency. We assessed the efficacy, safety, and immunogenicity of a candidate vaccine containing surface proteins from non-typeable *Haemophilus influenzae* (NTHi) and *Moraxella catarrhalis* (Mcat) in patients with COPD.

Methods This multicentre, randomised, observer-blinded, placebo-controlled, proof-of-concept, phase 2b trial recruited patients with stable COPD, moderate-to-very severe airflow limitation (Global Initiative for Chronic Obstructive Lung Disease [GOLD] stage 2, 3, or 4), at 67 clinical sites in Belgium, Canada, France, Germany, Italy, Spain, UK, and USA. Eligible patients were aged 40–80 years and had a history of at least one moderate or severe exacerbation in the previous year. Patients were allocated (1:1) using a minimisation algorithm to receive two intramuscular injections of NTHi–Mcat vaccine or placebo 60 days apart, in addition to standard care. The allocation algorithm considered age category, number of previous exacerbations, COPD severity at study entry, and country as minimisation factors, to guarantee treatment balance within each factor. Vaccine recipients and those responsible for evaluating study endpoints were masked to group allocation. In the analysis of efficacy, the primary outcome was the rate of any moderate or severe AECOPD occurring within a 1-year period, starting 1 month after the second dose in patients who received two vaccine doses (modified total vaccinated cohort). Safety was assessed in the total vaccinated cohort. The trial is registered with ClinicalTrials.gov, number NCT03281876, and is complete.

Findings Between Nov 27, 2017, and Nov 30, 2018, 606 adults were enrolled and included in the total vaccinated cohort (304 in the NTHi–Mcat vaccine group, 302 in the placebo group); 571 received two doses and were included in the primary efficacy analysis (279 in the NTHi–Mcat vaccine group, 292 in the placebo group). 23 participants dropped-out in the NTHi–Mcat vaccine group and 39 in the placebo group; this included 4 patients in the NTHi–Mcat vaccine group and 15 in the placebo group who withdrew from the study because of an adverse event. The primary analysis included 340 exacerbations (in follow-up time 102 123 days) in the NTHi–Mcat vaccine group and 333 (in 104 443 days) in the placebo group, with a yearly rate of moderate or severe AECOPD of 1·22 in the NTHi–Mcat vaccine group and 1·17 in the placebo group, with vaccine efficacy in reducing the yearly rate of moderate or severe AECOPD estimated to be zero (vaccine efficacy point estimate 2·26% [87% CI –18·27 to 11·58]; p=0·82). Solicited local adverse events were more frequent in the NTHi–Mcat vaccine group (216 [72%] of 301 patients) than with placebo (34 [11%] of 299 patients), and the frequency of solicited general adverse events was similar between groups (239 [79%] of 301 *vs* 235 [79%] of 299 patients). There was one death in the NTHi–Mcat vaccine group (acute respiratory failure, not related to vaccination) and ten in the placebo group (seven due in part to COPD or respiratory failure). There were 158 serious adverse events (89 [29%] of 304 patients) in the NTHi–Mcat vaccine group, not related to vaccination, and 214 (99 [33%] of 302 patients) in the placebo group.

Interpretation NTHi–Mcat vaccine administered to patients with COPD did not show efficacy in reducing the yearly rate of moderate or severe exacerbations. No safety concerns were identified.

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See **Online** for appendix

Research in context

Evidence before this study

Non-typeable *Haemophilus influenzae* (NTHi) and *Moraxella catarrhalis* (Mcat) are common pathogens in acute exacerbations of chronic obstructive pulmonary disease (AECOPD). We searched PubMed and ClinicalTrials.gov for studies of vaccination to prevent AECOPD associated with NTHi and Mcat, published from database inception up to Oct 12, 2021, with no restrictions on type of study. We used the terms ("COPD") AND ("vaccine") AND ("clinical trials") with no language restrictions. We identified one study of our own candidate NTHi–Mcat vaccine and three studies of related NTHi vaccine formulation. No safety concerns were identified in two studies of related investigational vaccine formulations containing three conserved surface proteins from NTHi and all formulations induced antigen-specific immune responses. One study of the related vaccine recruited 48 healthy adults aged 18–40 years and the second related vaccine study recruited 270 adults aged 50–70 years with a smoking history. The NTHi vaccine formulations that included the Adjuvant System AS01$_E$ produced the highest humoral and cellular immune responses in older adults (aged 50–70 years). In a study of 145 adults with COPD, the related adjuvanted NTHi vaccine had an acceptable safety profile and good immunogenicity. An exploratory analysis showed a non-significant lower rate of moderate or severe exacerbations in the NTHi vaccine group than with placebo (1·49 *vs* 1·73; p=0·44) in the 1-year period after the second dose. One study assessed a two-dose schedule of a vaccine containing the same NTHi surface proteins as in the investigational NTHi vaccine plus a conserved Mcat surface protein (NTHi–Mcat vaccine) when administered to 30 healthy adults aged 18–40 years and 90 adults aged 50–70 years with a smoking history. The formulation administered to the older age group was adjuvanted with AS01$_E$. The results with the adjuvanted NTHi–Mcat vaccine showed no safety concerns and good immunogenicity.

Added value of this study

This is the first time that a candidate NTHi–Mcat vaccine has been assessed in patients with COPD (moderate to very severe airflow limitation). The results showed no safety concerns with the vaccine and immunogenicity but did not show efficacy in reducing the yearly rate of moderate or severe exacerbations. Review of the safety data and efficacy results by exacerbation severity might suggest vaccination reduced the frequency of severe exacerbations and related hospitalisations, although the study was not powered to formally compare these endpoints between the two groups.

Implications of all the available evidence

There were no safety concerns with the NTHi–Mcat vaccine when given to patients with COPD and moderate to very severe airflow limitation, confirming results obtained in studies of healthy adults. The absence of efficacy against exacerbations despite immune response suggests better understanding is required of the heterogeneity of exacerbations and the immune mechanisms involved in acute exacerbations of COPD. Observations of a lower yearly rate of severe episodes and fewer reports of hospitalisations due to COPD in the NTHi–Mcat vaccine group than with placebo encourage further evaluation of this candidate vaccine.

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of death worldwide; in 2017, this disease was associated with 3·2 million deaths, an increase of 17·5% from 2007.[1] COPD is characterised by episodes of acute worsening of respiratory symptoms (exacerbations) that have considerable adverse consequences for patients, particularly among those experiencing frequent exacerbations.[2–5] Acute exacerbations of COPD (AECOPD) are heterogeneous with respect to cause, pathophysiological mechanisms, underlying inflammation, symptoms, and severity.[2]

Bacterial infection is considered a major cause of exacerbations, with non-typeable *Haemophilus influenzae* (NTHi), *Moraxella catarrhalis* (Mcat), and *Streptococcus pneumoniae* among the most frequent bacteria identified in AECOPD.[6–9] Long-term use of prophylactic antibiotics to mitigate bacteria-associated exacerbations as an option for selected patients has limited applicability because of the risk of antibiotic resistance and adverse effects.[3,10,11] Innovative approaches towards preventing exacerbations caused by bacterial infection are therefore an important area of COPD research, including vaccine development. No vaccine has been developed or is indicated for preventing AECOPD.

NTHi and Mcat appear to be co-pathogens in respiratory tract infections and COPD. Evidence suggests that Mcat produces complement resistance factors on outer membrane vesicles that might protect NTHi from complement-mediated killing,[12] and that NTHi and Mcat co-infections promote increased resistance to antibiotics and host clearance.[13,14] An adjuvanted multicomponent vaccine has been developed to reduce the frequency of moderate or severe AECOPD associated with NTHi and Mcat. The investigational NTHi–Mcat vaccine contains four surface proteins involved in the virulence mechanisms of both bacterial pathogens:[15] three proteins are from NTHi, a free recombinant protein D and a recombinant fusion protein combining protein E and pilin A (PE–PilA), and the fourth from Mcat, ubiquitous surface protein A2 (UspA2). The investigational vaccine also contains Adjuvant System AS01$_E$.[15] The Adjuvant System (AS) approach combines two or more different immunostimulants to achieve the desired response, since vaccines formulated with single adjuvants do not always

induce the required immune response to overcome vaccine development challenges.[16]

The NTHi–Mcat vaccine formulation containing $AS01_E$, 10 µg protein D, 10 µg PE–PilA, and 3·3 µg UspA2 had an acceptable safety profile and good immunogenicity up to 12 months after the second vaccine dose when administered in a two-dose schedule to older adults (aged 50–70 years) with a smoking history to represent the COPD population.[15] In the present phase 2b trial, we evaluated the efficacy, safety, and immunogenicity of this NTHi–Mcat vaccine formulation in patients aged 40–80 years with COPD and a history of acute exacerbations.

Methods

Study design and patients

This was a proof-of-concept, multicentre, observer-blinded, placebo-controlled, phase 2b trial conducted at 67 clinical sites in Belgium, Canada, France, Germany, Italy, Spain, UK, and USA. Patients with stable COPD were recruited at clinical sites according to the enrolment criteria listed in the study protocol, a link to which is provided in the appendix (appendix p 3).

Eligible patients were aged 40–80 years with a diagnosis of COPD[3] and documented history of at least one moderate or severe AECOPD in the previous 12 months. The last exacerbation had been resolved for at least 30 days at the time of first vaccination. Patients had a post-bronchodilator FEV_1 over forced vital capacity ratio (FEV_1/FVC) of less than 0·7 and FEV_1 of less than 80% predicted normal. The degree of airflow limitation was defined as moderate, severe, or very severe (grade 2, 3, or 4), according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) grading.[3] A documented history of moderate or severe AECOPD was defined as a medical record of worsening COPD symptoms that required oral corticosteroids, antibiotics, or both (moderate exacerbation) or hospitalisation (severe). Complete inclusion and exclusion criteria are listed in the study protocol (appendix p 3). Maintenance inhaled corticosteroid and long-acting bronchodilator use was permitted according to local treatment recommendations. Chronic antibiotic treatment for the prevention of exacerbations was not permitted.

The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. The protocols and associated documents were reviewed and approved by the ethics committee of each participating centre. All participants provided written informed consent before study entry.

Randomisation and masking

Patients were allocated to receive two doses of NTHi–Mcat vaccine or placebo 60 days apart, in addition to standard care, using a minimisation algorithm (1:1 ratio between treatments) that considered age category (40–59 or 60–80 years), number of previous exacerbations (<2 or ≥2), severity of airflow limitation at study entry (GOLD grade 2, 3, or 4), and country as factors. All factors had equal weight in the minimisation algorithm. The randomisation of supplies was performed at GSK using MATerial Excellence (MATEX), a program developed by GSK (Belgium) for use with Statistical Analysis Systems (SAS) software.

Due to differences in the appearance of the study vaccine and placebo formulation, and because the vaccine was prepared on site, the trial was conducted in an observer-blinded manner—ie, formulation recipients and those responsible for evaluating any study endpoint were unaware of whether vaccine or placebo was administered, and each formulation was prepared and administered by medical personnel who did not participate in any of the study's clinical evaluations or assays.

Procedures

Patients received intramuscular injections of two doses of the candidate NTHi–Mcat vaccine or placebo given 60 days apart (appendix p 14). Placebo was in the form of phosphate-buffered saline. The NTHi–Mcat vaccine contained 10 µg protein D, 10 µg PE–PilA, and 3·3 µg UspA2, and included Adjuvant System $AS01_E$, containing 3-O-desacyl-4′-monophosphoryl lipid A (MPL), QS-21 (*Quillaja saponaria* Molina, fraction 21; licensed by GSK from Antigenics LLC, a wholly owned subsidiary of Agenus Inc, a Delaware USA corporation) and liposome (25 µg MPL and 25 µg QS-21).[17] The NTHi and Mcat antigens have been described previously.[15,18]

Patients were asked to record COPD symptoms in their electronic diary cards each morning and evening. Additional visits took place within 96 h of onset of potential exacerbation symptoms. An exacerbation was defined, based on modified Anthonisen criteria,[19,20] as worsening of at least two major symptoms (dyspnoea, sputum volume, and sputum purulence) for at least 2 consecutive days, or worsening of any major symptom together with any of the following minor symptoms for at least 2 consecutive days: sore throat, cold (nasal discharge or nasal congestion), fever (oral temperature ≥37·5°C), increased cough, and increased wheeze. Each exacerbation was confirmed clinically by the investigator, whether identified by electronic diary card or reported directly by the patient. Exacerbation severity was defined by the investigator as mild (controlled with an increased dosage of regular medications), moderate (treated with systemic or oral corticosteroids or antibiotics), or severe (hospitalisation required).

Patients were asked to report solicited local (pain, redness, and swelling at the injection site) and general (chills, fatigue, fever, gastrointestinal symptoms, headache, and myalgia) adverse events for 7 days after each dose on electronic diary cards, and investigators reported unsolicited adverse events for 30 days after each dose on electronic case report forms. Data on potential immune-mediated disorders (including autoimmune and other inflammatory or neurologic disorders)[21] and serious adverse events were collected throughout the trial.

For **study results** see https://www.clinicaltrials.gov/ct2/show/results/NCT03281876?term=NCT03281876&draw=2&rank=1&view=results

Sputum samples were collected before first vaccination, 30 days after second vaccination, and 4, 7, 10, and 13 months after second vaccination, and at each AECOPD visit from first vaccination to study conclusion. Sputum samples were obtained by spontaneous expectoration or induced and were processed according to standard methods (appendix p 3). Quantitative PCR was used to detect and quantify *Haemophilus influenzae* and Mcat (appendix p 3). From available epidemiological data,[8] it was assumed that more than 99% of *H influenzae* detected by PCR in sputum were NTHi.

Blood samples were collected for the assessment of humoral immunogenicity before each vaccination, 30 days after each vaccination, 7 and 13 months after second vaccination, and at each AECOPD visit from first vaccination to study conclusion. Immunoglobulin G antibody levels to each vaccine antigen were measured by ELISA, developed, and at least qualified by GSK laboratories in Rixensart, Belgium. Four ELISAs were used, one for each antigen (protein D, protein E, PilA, and UspA2). Sera were stored at –20°C or below until assayed. Standardised procedures and in-house-made reference serum were used for each assay. The assay cutoff (lower limit of quantification) was 153 ELISA units (EU)/mL for anti-protein D, 16 EU/mL for anti-protein E, 8 EU/mL for anti-PilA, and 28 EU/mL for anti-UspA2. Protective antibody threshold levels for NTHi and Mcat are not yet known.

Blood samples for cell-mediated immune response analysis were taken before vaccination, 30 days after second vaccination, and 7 and 13 months after second vaccination in a subset of patients (around 60 patients per group). Cell-mediated immune responses (antigen-specific $CD4^+$ T cells) were measured by flow cytometry using intracellular cytokine staining on peripheral blood mononuclear cells, following an adaptation of previously described methods.[22] Numbers of antigen-specific $CD4^+$ T cells expressing at least two different markers amongst CD40 ligand (CD40L), interleukin (IL)-2, tumour necrosis factor (TNF), interferon (IFN)-γ, IL-13, and IL-17 were calculated.

Outcomes

The primary objective of the trial was to assess the efficacy of the candidate NTHi–Mcat vaccine compared with placebo in reducing the rate of moderate or severe exacerbations in patients with COPD at 1 year after the second vaccine dose. Other efficacy endpoints, safety and reactogenicity, and humoral and cellular immunogenicity of the NTHi–Mcat vaccine were investigated as secondary or tertiary objectives.

The primary outcome was the rate of moderate or severe AECOPD (any cause) occurring within a period starting 1 month after the second vaccine dose and lasting 1 year. 25 secondary outcome endpoints were evaluated, as detailed in the study protocol (appendix p 3); ten (three efficacy outcomes for moderate or severe AECOPD and all safety and immune response outcomes) are described in this first report from this trial. Study results including all other secondary efficacy outcomes can be found at ClinicalTrials.gov (NCT03281876). Secondary outcomes included the yearly rate of all AECOPD (any cause, categorised by severity) occurring within a period starting 1 month after the second vaccine dose (including the rate of AECOPD in 3-month observation periods), time to first AECOPD (categorised by severity), and duration of AECOPD (categorised by severity); rate of AECOPD (categorised by severity), time to first AECOPD (categorised by severity), and duration of AECOPD (categorised by severity) associated with bacterial presence (NTHi or Mcat); and immunogenicity (humoral and cell-mediated). Other secondary outcomes were occurrences of solicited local and general adverse events during the 7-day follow-up period after vaccination, any unsolicited adverse events during the 30-day follow-up period after vaccination, and any potential immune-mediated disorder or serious adverse events (any untoward medical occurrence that resulted in death or disability, was life-threatening, or required hospitalisation or prolongation of hospitalisation) from first vaccination to study end. Adverse event intensity was graded on a 1–3 scale. Grade 3 intensity was defined as redness or swelling of diameter or greater than 100 mm, temperature 39·0°C or higher, and, for all other adverse events, prevention of normal activities. All unsolicited adverse events, potential immune-mediated disorders, and serious adverse events were classified using preferred terms created using Medical Dictionary for Regulatory Activities (MedDRA) adverse reaction terminology.

Statistical analysis

Sample size was based on the probability to detect a clinically relevant effect.[23] The expected yearly incidence rate of moderate or severe AECOPD in the placebo group was 0·8 per patient[24,25] and expected over-dispersion parameter was 1·8. Approximately 300 patients per group were required to have 80% power to detect at least a 28% reduction in the rate of moderate or severe AECOPD in the NTHi–Mcat vaccinated group compared with the placebo group (appendix p 4), with a one-sided 6·5% significance level and dropout rate of 15%.

The populations included in the different analyses are described in the appendix (p 3). The primary efficacy analysis was performed on a modified total vaccinated cohort that included patients who received two vaccine doses and had been followed for at least 1 month after the second dose. Vaccine efficacy was defined as $(1-[R_{Vaccine}/R_{Placebo}])*100$, where $R_{vaccine}$ is the yearly rate of moderate or severe AECOPD in the NTHi–Mcat vaccine group and $R_{placebo}$ is the yearly rate of moderate or severe AECOPD in the placebo group. It was planned to evaluate the primary objective with an alpha level of 13% and thus, together with the point estimate, the 87% CI was computed as primary evaluation for efficacy. The 95% CI

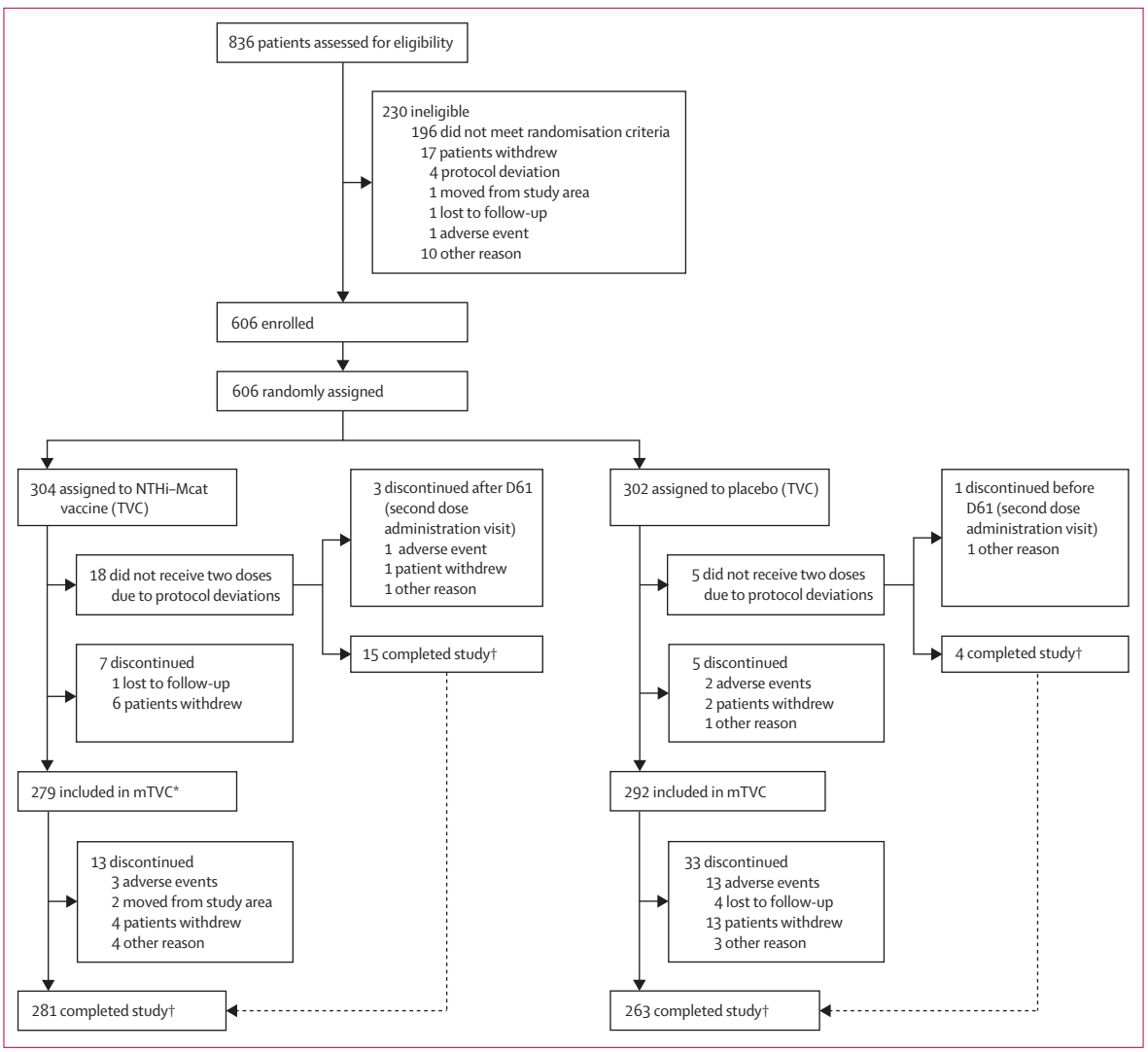

Figure 1: **Trial profile**
Mcat=*Moraxella catarrhalis*. NTHi=non-typeable *Haemophilus influenzae*. mTVC=modified total vaccinated cohort (patients who received two vaccine doses and had been followed up for at least 1 month after the second dose). TVC=total vaccinated cohort. *One patient left the study after receiving the second dose but before follow-up started at 1 month after the second dose and so was not included in efficacy analysis. †Subject who returned for the concluding visit (D451) foreseen in the protocol was considered to have completed the study.

was also reported. No alpha adjustment was performed as there was only one primary endpoint. All secondary endpoints were exploratory (no alpha adjustment) and interpreted descriptively.

The primary criterion to conclude vaccine efficacy in preventing moderate or severe exacerbations was a lower limit of the two-sided 87% CI above 0. The inferential model for vaccine efficacy used a negative binomial regression, with number of exacerbations as dependent variable, treatment (vaccine or placebo), age group (40–59 or 60–80 years), GOLD grade (2, 3, or 4), history of moderate or severe exacerbations (<2 or ≥2), and country as independent variables, with logarithm as link function, and the logarithm of time for follow-up (in days) as an offset variable.

Yearly rates of AECOPD according to each severity stratification, occurring from enrolment up to 1 month after the second dose, and incidence rates and vaccine efficacy in the prevention of AECOPD in the 1-year period starting 1 month after the second dose were calculated with 95% CIs using the same negative binomial models without covariates. The duration (in days) of AECOPD was evaluated via descriptive statistics (no inference was planned). Time to first exacerbation event from 1 month after the second dose was analysed using Cox's proportional hazard regression model with treatment, GOLD grade at enrolment, and history of exacerbations as factors. Kaplan-Maier curves and hazard rate with 95% CI were reported. Vaccine efficacy was calculated for subgroups categorised by baseline GOLD

	NTHi–Mcat vaccine group (n=279)	Placebo group (n=292)
Age at enrolment, years		
Mean	65·9 (7·4)	66·3 (7·2)
Median	66·0	67·0
Age group		
40–59 years	56 (20%)	60 (21%)
60–80 years	223 (80%)	232 (79%)
Sex		
Male	165 (59%)	169 (58%)
Female	114 (41%)	123 (42%)
Race		
Black or African American	4 (1%)	3 (1%)
American Indian or Alaska Native	0	1 (0%)
Asian, Central or South Asian Heritage	1 (0%)	0
Asian, South East Asian Heritage	0	1 (0%)
White, Arabic or North African Heritage	2 (1%)	0
White, Caucasian or European Heritage	271 (97%)	287 (98%)
Other	1 (0%)	0
Ethnicity		
Hispanic or Latino	0	3 (1%)
Not Hispanic or Latino	278 (100%)	288 (99%)
Missing data	1 (0%)	1 (0%)
Smoking status		
Current	83 (30%)	111 (38%)
Former	196 (70%)	181 (62%)
Inhaled corticosteroid usage		
Before 1 month after second dose	203 (73%)	225 (77%)
GOLD grade		
2	111 (40%)	127 (43%)
3	126 (45%)	124 (43%)
4	42 (15%)	41 (14%)
Number of moderate and severe exacerbations in the previous 12 months		
<2	134 (48%)	137 (47%)
≥2	145 (52%)	155 (53%)
FEV_1/FVC ratio		
Missing data	0	1 (0%)
<70	278 (100%)	289 (99%)
≥70	1 (0%)	2 (1%)

Data are n (%), mean (SD), median (IQR). FVC=forced vital capacity. GOLD=Global Initiative for Chronic Obstructive Lung Disease. Mcat=*Moraxella catarrhalis*. NTHi=non-typeable *Haemophilus influenzae*.

Table 1: **Baseline characteristics (modified total vaccinated cohort)**

spirometric grade, country, history of exacerbations, and age group. Post-hoc analyses were also done for subgroups categorised according to usage of inhaled corticosteroid at the first study visit and blood eosinophil level at baseline.

Analysis of solicited local and general adverse events included all patients with at least one dose of vaccine or placebo administered and who provided solicited safety data during the 7-day reporting period. Analysis of unsolicited adverse events during the 30-day follow-up period after vaccination, and any potential immune-mediated disorders or serious adverse events during the entire study, included all patients who received at least one dose of vaccine or placebo. The incidence of adverse events per study group was calculated with exact 95% CIs.

Within each group, antibody geometric mean concentrations (GMCs) in the total vaccinated cohort were determined with 95% CIs, and differences between groups were estimated using an analysis of covariance model on the logarithm base 10 transformation of ELISA concentrations. The model included group (vaccine or placebo) as factor, age category, GOLD grade, and country as fixed effects and concentration before the first dose as covariate. Cell-mediated immune response data are presented for a subset of patients who received vaccine or placebo according to protocol. The frequency was calculated of antigen-specific $CD4^+$ T cells expressing at least two markers upon in-vitro stimulation with the relevant antigen presented in a peptide pool, after subtraction of the corresponding frequency of $CD4^+$ T cells similarly stimulated with medium instead of the peptide pool (background frequency). The frequency of specific $CD4^+$ T cells was summarised using descriptive statistics.

The statistical analyses were performed using SAS within the Life Science Analytics Framework system. The trial was registered with ClinicalTrials.gov, number NCT03281876.

Role of the funding source

The funder of the study, GlaxoSmithKline Biologicals SA, contributed to study design, data collection, data analysis, data interpretation, and writing of the report. GlaxoSmithKline Biologicals SA also covered all costs associated with the development and publication of this manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Nov 27, 2017, and Nov 30, 2018, 606 adults with confirmed COPD and a history of moderate or severe AECOPD were recruited, received at least one dose of study vaccine, and were included in the total vaccinated cohort for the analysis of safety. A total of 281 patients in the NTHi–Mcat vaccine group and 263 in the placebo group completed the planned follow-up, with 23 and 39 dropouts, respectively (figure 1). Of the patients who dropped-out of the study, four patients in the NTHi–Mcat vaccine group and 15 in the placebo group withdrew because of an adverse event. The primary analysis population (modified total vaccinated cohort) included 571 patients who received two doses (279 in NTHi-Mcat

vaccine group, 292 in placebo group; figure 1). Patients' baseline characteristics were well balanced between groups (table 1); 271 (47%) had a history of one moderate or severe exacerbation and 300 (52%) had at least two moderate or severe exacerbations in the year before enrolment.

The primary analysis for vaccine efficacy included 340 exacerbations (in total follow-up time 102 123 days) in the vaccine group and 333 exacerbations (in 104 443 days) in the placebo group. The yearly rate of moderate or severe AECOPD (starting 1 month after the second dose) was 1·22 in the NTHi–Mcat vaccine group and 1·17 in the placebo group. Vaccine efficacy in reducing the yearly rate of moderate or severe AECOPD was estimated to be zero, with a point estimate of –2·26% (87% CI –18·27 to 11·58; 95% CI –23·45 to 15·29; figure 2) for the vaccine group versus the placebo group. The hazard ratio for risk of having a moderate or severe AECOPD relative to the placebo group was 0·94 (95% CI 0·76 to 1·17) for the NTHi–Mcat vaccine group, and there was no significant difference between groups in time to first moderate or severe exacerbation (p=0·58) and no significant effect by log-rank test (p=0·58; appendix p 15).

All other analyses were not powered and no alpha adjustment was made. Vaccine efficacy estimates for mild, moderate, and severe exacerbations are shown in the appendix (p 7). The point estimate for vaccine efficacy in reducing severe episodes was 36·54% (95% CI –4·69 to 61·53; appendix p 7). The hazard ratio for relative risk of having a severe AECOPD was 0·72 (95% CI 0·45 to 1·16) for the NTHi–Mcat vaccine group (p=0·18; appendix p 8).

Vaccine efficacy for moderate or severe AECOPD was similar (overlapping 95% CIs) in analyses by follow-up category and by baseline GOLD grade, exacerbation frequency, age group, and country (figure 3). Analysis of moderate or severe AECOPD by 3-month follow-up period showed no reduction in yearly rate. The point estimate for vaccine efficacy on severe episodes was 75·82% (95% CI 27·20 to 91·97) at 9–12 months from 1 month after the second dose (appendix p 9). Post-hoc analysis of patients categorised by inhaled corticosteroid use and blood eosinophil level at baseline showed no reductions in yearly rate of moderate or severe AECOPD (figure 3).

Sputum samples were available for 399 exacerbations that occurred after 1 month after the second dose (215 in 116 patients in the NTHi–Mcat vaccine group, 184 in 118 patients in the placebo group). Few sputum samples were analysed from patients with severe AECOPD (six in NTHi–Mcat vaccine group, four in placebo group) because of missed study visits due to hospitalisations. The rate of moderate or severe AECOPD associated with NTHi or Mcat, or both, as detected by PCR, was 0·32 (per person in 1 year) in both groups. *H influenzae* was detected in 76 (35%) exacerbation samples in the NTHi–Mcat vaccine group and 85 (46%) exacerbation samples in the placebo group. Mcat was detected in 53 (25%) and 37 (20%) samples, respectively. There was no difference between groups in bacterial load at the first study visit, any AECOPD visit, or post-vaccination stable visit (data not shown).

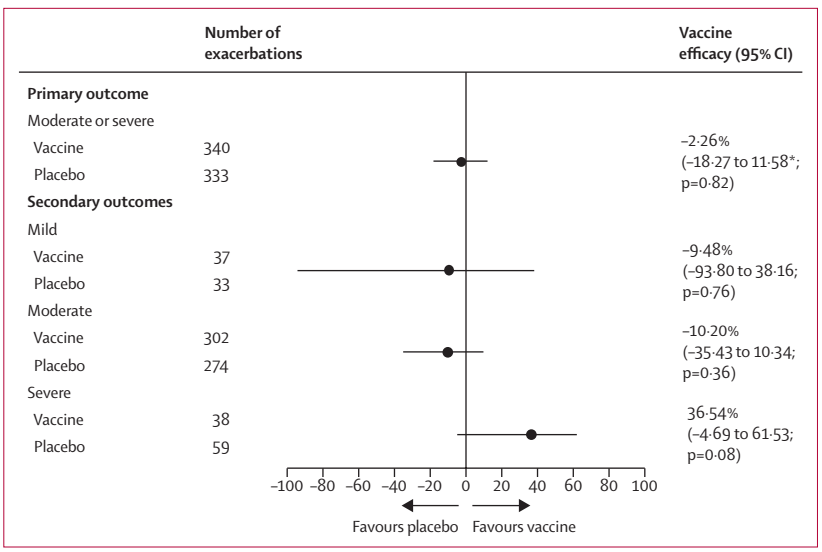

Figure 2: **Vaccine efficacy against AECOPD by exacerbation severity (modified total vaccinated cohort; n=571)**
AECOPD=acute exacerbations of chronic obstructive pulmonary disease. *87% CI for moderate or severe category (95% CI for this endpoint was –23·45 to 15·29). Vaccine efficacy in preventing moderate or severe exacerbations was concluded if the lower limit of the two-sided 87% CI was above 0.

Data for solicited local and general reactions from completed electronic diary cards 7 days after vaccination was available for analysis in 301 patients in the NTHi–Mcat vaccine group and 299 in the placebo group. Solicited local adverse events were more frequent in the NTHi–Mcat vaccine group (reported by 216 [72%] of 301 patients) than in the placebo group (34 [11%] of 299 patients), with a slight increase in reports after the second vaccine dose (appendix p 12). Pain was the most frequent solicited local adverse event during the 7-day post-vaccination period in each group (table 2; appendix p 16). Incidences of other individual solicited local adverse events were higher in the vaccine group than with placebo (table 2; appendix p 16). The frequency of solicited general adverse events was 79% (239 patients) in the vaccine group and 79% (235 patients) in the placebo group. There was no increase in reports of solicited general adverse events after the second vaccine dose (appendix p 12). The most frequent solicited general adverse event was fatigue; the incidences of all individual solicited general adverse events were similar between groups (table 2; appendix p 16). Grade 3 solicited local adverse events did not last longer than 3 consecutive days and grade 3 solicited general adverse events did not last longer than 6 consecutive days in both groups.

Safety was assessed in the total vaccinated cohort, comprising 304 patients in the NTHi–Mcat vaccine group and 302 in the placebo group. During the 30-day post-vaccination period, at least one unsolicited adverse event

	NTHi–Mcat vaccine, n/N	Placebo, n/N	Vaccine efficacy (95% CI)
All patients	**340/278**	**333/292**	**–2·26% (–23·45 to 15·29; p=0·82)**
6-month follow-up period after second dose			
0–6 months	181/278	183/292	–3·05% (–29·36 to 17·91; p=0·80)
6–12 months	159/272	150/280	–4·66% (–33·49 to 17·95; p=0·71)
3-month follow-up period after second dose			
0–3 months	92/278	82/292	–17·48 (–58·26 to 12·80; p=0·29)
3–6 months	89/274	101/288	7·00 (–23·74 to 30·10; p=0·62)
6–9 months	91/272	81/280	–12·64 (–52·04 to 16·55; p=0·44)
9–12 months	68/271	69/272	2·32 (–36·64 to 30·17; p=0·89)
GOLD grade			
2	103/111	118/127	8·42% (–19·8 to 29·99; p=0·52)
3	184/125	156/124	–17·05% (–45·16 to 5·62; p=0·15)
4	53/42	59/41	4·55% (–39·89 to 34·88; p=0·81)
Exacerbation history			
<2	130/133	136/137	12·27% (–18·93 to 35·29; p=0·40)
≥2	210/145	197/155	–14·02% (–44·26 to 9·88; p=0·27)
Age group			
40–59 years	77/55	74/60	–12·74% (–66·80 to 23·80; p=0·55)
60–80 years	263/223	259/232	0·63% (–22·74 to 19·56; p=0·95)
ICS usage			
No	74/76	58/67	–0·28% (–47·50 to 31·82; p=0·99)
Yes	266/202	275/225	–4·88% (–30·12 to 15·46; p=0·66)
Eosinophils level			
>150 mL	236/188	205/173	–4·44% (–32·72 to 17·81; p=0·72)
≤150 mL	86/81	111/109	3·76% (–31·73 to 29·69; p=0·81)
Frequent exacerbator			
Yes	233/164	223/177	–11·76% (–39·78 to 10·65; p=0·33)
No	107/114	110/115	9·27% (–26·37 to 34·86; p=0·56)
Country			
Belgium	15/15	16/17	0·10% (–174·95 to 63·70; p=0·99)
Canada	90/46	69/45	–30·85% (–86·08 to 7·99; p=0·13)
France	9/16	20/20	29·72% (–56·03 to 68·35; p=0·39)
Germany	57/56	45/56	–4·63% (–77·39 to 38·29; p=0·87)
Italy	7/18	13/16	68·48% (–9·29 to 90·91; p=0·07)
Spain	33/23	34/28	–21·89% (–99·36 to 25·48; p=0·43)
UK	45/32	59/33	22·54% (–22·14 to 50·88; p=0·27)
USA	84/72	77/77	–3·92% (–59·92 to 32·47; p=0·86)

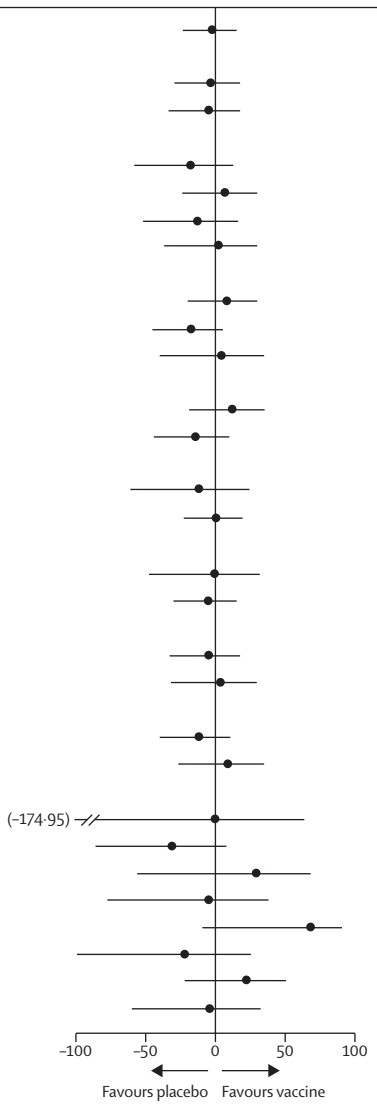

Figure 3: **Forest plot of vaccine efficacy for moderate and severe AECOPD in each subgroup analysis for 1 year starting from 1 month after the second dose (modified total vaccinated cohort; n=571)**

Subgroups are based on patient status at baseline, except for the 6 month and 3 month follow-up groups. Exacerbation history is the number of moderate and severe exacerbations in the previous 12 months and frequent exacerbators had 2 or more moderate or severe exacerbations or 1 or more severe exacerbation in previous 12 months. AECOPD=acute exacerbations of chronic obstructive pulmonary disease. n=number of exacerbations in a given arm. N=number of patients in the modified total vaccinated cohort. GOLD=Global Initiative for Chronic Obstructive Lung Disease. ICS=inhaled corticosteroid.

was reported by 110 (36%) of 304 patients (174 events) in the NTHi–Mcat vaccine group and 103 (34%) of 302 patients (182 events) in the placebo group, most commonly nasopharyngitis (all mild or moderate and unrelated to vaccination), reported by 13 (4%) patients in each group (13 events in NTHi–Mcat vaccine group, 15 in placebo group). The only other unsolicited adverse events reported by 3% or more of patients were diarrhoea (three reports in three [1%] of 304 patients in NTHi–Mcat vaccine group, ten in nine [3%] of 302 patients in the placebo group) and COPD according to MedDRA primary system organ class and preferred term (eight reports in eight [3%] of 304 patients and 12 reports in nine [3%] of 302 patients, respectively). Most unsolicited adverse events were mild or moderate, with 13 (4%) patients in the NTHi–Mcat vaccine group and 19 (6%) in the placebo group reporting severe symptoms. Unsolicited adverse events considered related to study vaccination were reported by nine (3%) patients (16 events) in the NTHi–Mcat vaccine group and eight (3%) patients (nine events) in the placebo group. There were 149 unsolicited adverse events leading to hospitalisation reported by 86 (28%)

	NTHi-Mcat vaccine group (n=301)	Placebo group (n=299)
Local		
Any local adverse event	216 (72% [66–77])	34 (11% [8–16])
Pain		
Any	209 (69% [64–75])	28 (9% [6–13])
Grade 3*	6 (2% [1–4])	0 (0% [0–1])
Redness		
Any	43 (14% [11–19])	1 (0% [0–2])
>100 mm	3 (1% [0–3])	0 (0% [0–1])
Swelling		
Any	34 (11% [8–15])	2 (1% [0–2])
>100 mm	5 (2% [1–4])	0 (0% [0–1])
General		
Any general event	239 (79% [74–84])	235 (79% [74–83])
Chills		
Any	52 (17% [13–22])	52 (17% [13–22])
Grade 3	3 (1% [0–3])	1 (0% [0–2])
Fatigue		
Any	193 (64% [58–70])	197 (66% [60–71])
Grade 3	18 (6% [4–9])	17 (6% [3–9])
Fever†		
Any	39 (13% [9–17])	32 (11% [7–15])
Grade 3	4 (1% [0–3])	2 (1% [0–2])
Gastrointestinal symptoms‡		
Any	71 (24% [19–29])	77 (26% [21–31])
Grade 3	0 (0% [0–1])	2 (1% [0–2])
Headache		
Any	126 (42% [36–48])	109 (37% [31–42])
Grade 3	1 (0% [0–2])	4 (1% [0–3])
Myalgia		
Any	114 (38% [32–44])	94 (31% [26–37])
Grade 3	5 (2% [1–4])	5 (2% [1–4])

Data are n (% [95% CI]). NTHi=non-typeable *Haemophilus influenzae*. Mcat=*Moraxella catarrhalis*. *Grade 3 defined as diameter >100 mm (redness and swelling), temperature ≥39·0°C (fever), or preventing normal activity (pain, fatigue, headache, chills, myalgia, gastrointestinal symptoms). †Fever defined as temperature ≥37·5°C. ‡Gastrointestinal symptoms defined as nausea, vomiting, diarrhoea, or abdominal pain.

Table 2: **Solicited local and general adverse events during the 7-day follow-up period after vaccination (solicited total vaccinated cohort)**

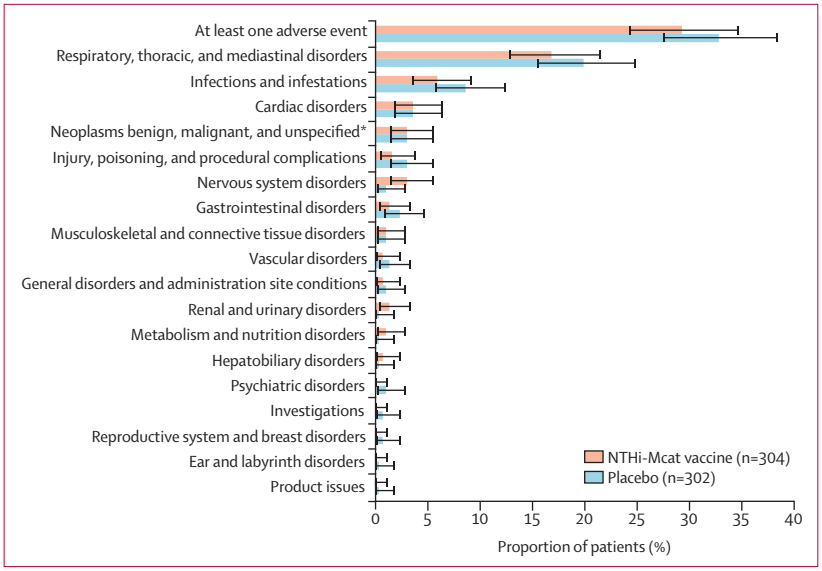

Figure 4: **Serious adverse events, by Medical Dictionary for Regulatory Activities (MedDRA) primary system organ class (total vaccinated cohort; n=606)**

Error bars are 95% CI. One death in vaccine group (due to acute respiratory failure; not considered related to study vaccination) and ten in placebo group (two deaths due to COPD; one due to infective COPD exacerbation; one due to COPD, respiratory failure, pneumonia, colon cancer, and anastomotic complication; one due to respiratory failure and intentional overdose; one due to acute respiratory failure, pneumonia, and sepsis; one due to pneumothorax, pneumonia, COPD, and alcohol withdrawal syndrome; one due to ileus; two due to cancer). COPD=chronic obstructive pulmonary disease. NTHi=non-typeable *Haemophilus influenzae*. Mcat=*Moraxella catarrhalis*. *Including cysts and polyps.

patients in the NTHi–Mcat vaccine group and 209 reported by 96 (32%) patients in the placebo group. The most common adverse events leading to hospitalisation were pneumonia (five events in five patients, 2%, in vaccine group; 17 events in 15 patients, 5%, in placebo group) and COPD (55 events in 41 patients, 14%, in vaccine group; 82 events in 53 patients, 18%, in placebo group); for all other events, there were maximum eight reports in seven patients (2%) in the vaccine group and maximum seven reports in seven patients (2%) in the placebo group.

During the entire study, there was one death in the NTHi–Mcat vaccine group (due to acute respiratory failure; not considered related to study vaccination) and ten in the placebo group (seven due at least in part to COPD or respiratory failure; figure 4). There were 158 serious adverse events reported by 89 (29%) patients in the NTHi–Mcat vaccine group and 214 serious adverse events reported by 99 (33%) patients in the placebo group (figure 4), most frequently pneumonia (five reports in five patients, 2%, in vaccine group; 17 reports in 15 patients, 5%, in placebo group), acute respiratory failure (eight reports in seven patients, 2%, in vaccine group; seven reports in seven patients, 2%, in placebo group), and COPD (55 reports in 41 patients, 14%, in vaccine group; 83 reports in 53 patients, 18%, in placebo group). Serious adverse events reported in 1% or more of patients were atrial fibrillation (five reports [1%] in vaccine group, two [1%] in placebo group); influenza (four reports [1%] in vaccine group, two [1%] in placebo group); pneumonia (five reports [2%] in vaccine group, 17 [5%] in placebo group); urinary tract infection (no reports in vaccine group, three [1%] in placebo group); transient ischaemic attack (three reports [1%] in vaccine group, no reports in placebo group); acute respiratory failure (eight reports [2%] in vaccine group, seven [2%] in placebo group); and COPD (55 reports [14%] in vaccine group, 83 [18%] in placebo group. Potential immune-mediated disease was reported for nine patients (six patients with ten events in NTHi–Mcat vaccine group, three patients with three events in placebo group). None of the serious adverse events or potential immune-mediated disease reports were considered related to vaccination.

The analysis of humoral immunogenicity included 304 patients who received the NTHi-Mcat vaccine and 302 who received placebo. GMCs for anti-protein D, anti-protein E, and anti-PilA antibodies increased at 1 month after each vaccine dose and waned thereafter but remained higher than baseline (appendix p 17). Anti-UspA2 antibody GMCs at baseline were relatively high in both groups (490·3 EU/mL in the vaccine group and 571·4 EU/mL in the placebo group). There was an increase in anti-UspA2 antibody GMCs after each NTHi–Mcat vaccination followed by a decrease towards baseline value (appendix p 17).

The per-protocol analysis of cell-mediated immune response included 50 patients who received the NTHi–Mcat vaccine and 49 patients who received placebo. Overall, there was high variability in the number of specific $CD4^+$ T cells for each vaccine antigen at each time point and $CD4^+$ T cell responses were low (rarely above 590, the lower limit of quantification of the assay). Evaluation of the frequency of antigen-specific $CD4^+$ T cells expressing at least two different markers among CD40L, IL-2, TNF, IFN-γ, IL-13, and IL-17 showed increases from baseline up to 1 month after the second NTHi–Mcat vaccine dose (appendix p 18). No IL-13 expression was detected (appendix p 19).

Discussion

This study is the first to report efficacy results from a new approach towards preventing NTHi-associated and Mcat-associated exacerbations in patients with COPD. A summary of the key findings is provided in the appendix (p 13). Results from this placebo-controlled phase 2b trial show no safety concerns with the candidate NTHi–Mcat vaccine and immunogenicity was shown in patients with moderate to very severe COPD. This was consistent with the phase 1 study (12 months post dose 2) of the NTHi–Mcat vaccine administered to older adults aged 50–70 years with a smoking history.[15] A 4-year follow-up of the phase 1 study also showed no safety concerns.[26] The primary endpoint was not met as the vaccine did not show efficacy in reducing the yearly rate of moderate or severe exacerbations, which was 1·22 in the NTHi–Mcat vaccine group and 1·17 in the placebo group. Similar exacerbation rates have been reported in the placebo groups of other COPD trials.[27] A phase 2 trial of an $AS01_E$-adjuvanted vaccine containing the same NTHi components and no Mcat component, also administered to patients with COPD aged 40–80 years, showed estimated vaccine efficacy over 1 year of 13·3% (95% CI –24·2 to 39·5), which was not significant.[28] Vaccine efficacy was an exploratory endpoint, calculated on a restricted number of patients (73 in NTHi vaccine group, 71 in placebo group) with moderate or severe airflow limitation.[28]

Categorisation showed most exacerbations were moderate in severity in our study, confirming previous findings,[8] and indicated possible differences in incidence of exacerbation severity between groups. The vaccine efficacy estimate against severe episodes and the hazard ratio for relative risk of having a severe AECOPD suggested non-significant reductions for the NTHi–Mcat vaccinated group. Review of safety data from study start to end of follow-up showed 55 reports of COPD leading to hospitalisation in the NTHi–Mcat vaccine group versus 82 reports in the placebo group. However, no conclusions can be drawn from these observations, as the trial was not powered to find differences in measurements other than for the primary analysis. Further assessments of the severe episodes are ongoing.

The safety profile of the NTHi–Mcat vaccine in the present trial is in line with findings in phase 1, when the vaccine was administered to older adults with a smoking history.[15] This group was chosen to immunologically match the COPD population, given evidence that alterations in the immune system start early in smokers, before COPD is recognised.[29–31] The safety profile is also consistent with that of the vaccine containing the NTHi component only, as reported in phase 1 studies of healthy 18–40 year-olds and older smokers or ex-smokers (aged 50–70 years)[18] and in the phase 2 trial of patients with COPD.[28] In our study and the phase 1 study of the NTHi-Mcat vaccine,[15] there was a higher frequency of solicited local adverse events in the vaccinated group. These solicited local adverse events might be related to more intense activation of the innate immune response by AS-adjuvanted vaccines.[18,32] Most solicited adverse events were mild to moderate in intensity and grade 3 events were transient. During the entire trial, there was one death in the NTHi–Mcat vaccine group and ten in the placebo group. No serious adverse events were reported related to vaccination. Serious adverse events were reported by 89 patients in the NTHi–Mcat vaccine group and 99 patients in the placebo group, most frequently pneumonia (five reports in NTHi–Mcat vaccine group, 17 in placebo group) and COPD (55 and 83 reports, respectively). However, as the safety analysis was descriptive, it is not possible to determine a difference between groups.

Humoral immune responses to the NTHi antigens in the present trial were similar to those observed previously.[15,18,28] The vaccine induced persistent specific immune responses against the NTHi antigens up to 12 months after the second vaccine dose. The specific response against the Mcat antigen was transient, which might have been due to the relatively high concentrations of anti-UspA2 antibodies before vaccination, as also reported in phase 1.[15] The cell-mediated immunity results must be interpreted with caution due to the small number of patients included in this investigation. These results showed high variability, as reported previously.[15] Antigen-specific cell-mediated immune responses 1 month after the second dose, in terms of $CD4^+$ T cells expressing at least two markers, tended to be higher in the NTHi–Mcat vaccine group than with placebo, but responses overall were low.

This study had some limitations. Interpretation of the vaccine efficacy results of this trial is limited since the analysis did not take into account any changes in COPD therapy during the study that could have had an impact on the AECOPD rate, such as usage of inhaled corticosteroid therapy during the study. In the analysis of bacteria, only a small number of sputum samples were obtained from patients with severe AECOPD, who were generally unable to attend protocol-specified AECOPD visits due to hospitalisation. Further investigations are needed to understand why the primary outcome was not met, such as assessments of the role of exacerbation heterogeneity, particularly the roles of respiratory infection and persistent bacterial colonisation, underlying inflammation, immune mechanisms involved in AECOPD, and the immunogenicity of the vaccine antigens. Since the prevalence of NTHi and Mcat infection at exacerbation was consistent with the clinical assumptions for the study design, the observation of no difference in frequency of NTHi and Mcat infections between groups might suggest alternative correlates of protection are required or that changes in bacterial load modulate exacerbation severity, but this was not analysed. Alternatively, there might have been complex interplay between these bacteria and other components of the microbiome. Also, analyses are underway to examine vaccine efficacy in various subgroups, including against severe AECOPD and the investigation of any delayed vaccine effect, for which the mechanism is unclear given the lack of efficacy earlier in the study.

In conclusion, this phase 2b trial did not meet its primary efficacy objective of reducing the frequency of moderate or severe exacerbations when the NTHi–Mcat vaccine was administered in a two-dose schedule to patients with COPD. No safety concerns were identified and the results confirm the vaccine's immunogenicity. Observations suggesting possible reductions in the NTHi–Mcat vaccinated group in the yearly rate of severe exacerbations and related hospitalisations encourage further evaluation.

Contributors

SA, MT, HW, TMAW, DC, GDM, ML, LM, SS, AT, and AKA contributed to the study design and methods. SA, LB, GB, WJ, EK, AP, BP, LP-M, DS, HW, TMAW, and FM were responsible for the oversight of the study at their respective sites and contributed to the recruitment of participants. MT, DC, GDM, ML, LM, SS, AT, and AKA were responsible for data acquisition, data analysis, and data interpretation. All authors read and edited the manuscript. All authors approved the final version and the decision to submit the manuscript. MT, DC, and LM verified the underlying data in the study. All authors had full access to all the data and had final responsibility for the decision to submit for publication.

Declaration of interests

SA reports grants and personal fees from Boehringer Ingelheim, grants from Pfizer, and personal fees from Novartis, AstraZeneca, the GlaxoSmithKline (GSK) group of companies, Chiesi, and Merini, outside of the submitted work. AKA, DC, GDM, ML, LM, SS, and AT are employees of the GSK group of companies. MT was an employee of the GSK group of companies when this study was conducted and is now an employee of Janssen–Cilag SpA. ML and SS also hold shares in the GSK group of companies. GB reports having received honoraria for lectures from AstraZeneca, Boehringer Ingelheim, Chiesi, the GSK group of companies, Novartis, and Teva, and for advisory boards from Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, the GSK group of companies, Novartis, Sanofi–Regeneron, and Teva, all outside of the submitted work. WJ reports grants from AstraZeneca, Chiesi, Roche, and Boehringer Ingelheim outside of the submitted work. EK has served on advisory boards and received consulting fees and travel reimbursements from Amphastar, AstraZeneca, Boehringer Ingelheim, Chiesi, Connect Biopharmaceuticals, the GSK group of companies, Mylan, Novartis, Sunovion, and Theravance, outside of the submitted work. AP reports receiving fees for board membership, consultancy, payment for lectures, grants for research, travel expense reimbursement from Chiesi, AstraZeneca, the GSK group of companies, Boehringer Ingelheim, and Teva; fees for board membership, consultancy, payment for lectures, travel expense reimbursement from Mundipharma, Novartis, Zambon, and Sanofi–Regeneron; and grants for research, payment for lectures, travel expenses reimbursement from Menarini, fees for board membership, consultancy, travel expenses reimbursement from Roche, grants for research from Fondazione Maugeri, Fondazione Chiesi, and consultancy fees from Edmondpharma, all outside of the submitted work. LP-M reports, outside of the submitted work, financial support for educational activities and advisory from AstraZeneca, financial support for educational activities and a grant for non-committed investigation from the GSK group of companies, investigation grant from Esteve and Menarini, travel bourses from Boerhinger Ingelheim and Teva, travel bourse, and personal fees for educational activities from Novartis, financial support for educational activities from Chiesi, and personal fees for advisory from Merck Sharpe & Dohme and Boston Scientific. DS, BP, and LB declare no financial and non-financial relationships and activities and no conflicts of interest. HW reports a grant to his employer from the GSK group of companies during the conduct of this study, and grants or personal fees from the GSK group of companies, AstraZeneca, Boehringer Ingelheim, Novartis, Chiesi, Menarini, Takeda, and Bayer outside of the submitted work. TMAW received grants from the GSK group of companies during the conduct of this study. TMAW also received grants from AstraZeneca, Synairgen, UK Research and Innovation, and MyMHealth, and fees or non-financial support from Boehringer Ingelheim, Chiesi, and AstraZeneca, outside of the submitted work. TMAW is an inventor on patent applications: 2018 US Patent application 62/479562—immunogenic composition, use and methods of treatment—a novel vaccine to prevent exacerbations of COPD pending to the GSK group of companies; and US patent application 62/479550 (novel COPD vaccine). TMAW is the founder and director of MyMHealth Ltd. FM reports a grant paid to his institution by the GSK group of companies during the conduct of this study, and grants paid to his institution by the GSK group of companies, AstraZeneca, Sanofi; unrestricted grant paid to his institution by Novartis, Boehringer Ingelheim, Grifols; personal fees for participating in speaker bureau from the GSK group of companies, Boehringer Ingelheim, Grifols, Novartis; and financial participation in Oxynov, all outside of the submitted work.

Data sharing

Anonymised individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

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Vaccines for COPD exacerbation prevention: do they work?

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Exacerbations of chronic obstructive pulmonary disease (COPD) are a major cause of hospital admission, readmission, and mortality.[1] Thus exacerbation prevention is a priority to improve quality of life and reduce health-care costs. However, despite much effort by the respiratory research and pharmaceutical community, to date we have only a few interventions that reduce exacerbations and new approaches are urgently required.

Airway bacteria have been implicated as aetiological agents in exacerbations[2,3] and one of the targets for exacerbation prevention is to reduce bacterial load at exacerbation. However, patients with COPD have lower airway bacterial colonisation that increases with disease severity and this has been related to exacerbation frequency.[4] Thus a vaccine targeted at airway bacteria might act to either reduce bacterial load in the stable state or at exacerbation and thus prevent the exacerbation event.

In *The Lancet Respiratory Medicine*, Stefan Andreas and colleagues report the results of the first international study of a vaccine targeted at non-typeable *Haemophilus influenzae* (NTHi) and *Moraxella catarrhalis* (Mcat) with the objective of prevention of exacerbations in COPD.[5] The vaccine contains an adjuvant, requires two doses, and is targeted against four surface proteins responsible for bacterial virulence (three for NTHi and one for Mcat). The vaccine induced a persistent specific immune response against NTHi up to 12 months after the second vaccine dose, but the immune response was not so consistent against Mcat. T-cell responses were performed in smaller patient numbers and were more variable. Patients with COPD were selected with an exacerbation history but a variety of disease severities, although airway bacterial load is higher in patients with more severe disease and a vaccine is thus likely to be more effective in more severe COPD.

The primary outcome was the rate of moderate or severe COPD exacerbations occurring within a period starting 1 month after the second vaccine dose and lasting for 1 year. The exacerbation detection over the year was meticulous, but there was no difference in exacerbation rates between the vaccine and placebo groups. In the subgroup analyses, an interesting result was that the annual rate of severe exacerbations or related hospitalisations was reduced with the vaccine, although statistical significance was not reached. NTHi was detected in sputum at exacerbation in 35% of the vaccine group and 46% in the placebo group. Isolation of Mcat was lower and similar between the two groups. However, few samples were obtained from the patients with severe exacerbations as they were hospitalised and these samples would be more likely to have higher airway bacterial loads. *Streptococcus pneumoniae* is also an important airway bacterium,[6] but no information is provided on its isolation or how many patients in the trial had pneumococcal vaccination. The safety profile was good and only relatively mild local reactions were reported after vaccination.

Although the vaccine does seem to be effective with respect especially to NTHi and to the immune responses, the primary outcome was not met in the study and limited conclusions can be inferred from the secondary outcomes. However, it does seem as if the vaccine might be effective in preventing more severe exacerbations where bacteria are more likely to have an aetiological role. There is considerable debate on the role of airway bacteria at exacerbation and there is evidence from both experimental challenge[7] and clinical studies[8] that the initial exacerbation trigger is a respiratory virus and bacterial load increases as a secondary effect. This would thus limit the efficacy of a bacterial vaccine at exacerbation. However, airway bacteria have a more important role in colonising the airway and an increased bacterial load will increase airway inflammation[6] and thus increasing the susceptibility to exacerbations both viral and bacterial in aetiology. Because more severely affected patients with COPD generally develop more severe exacerbations,[9] an effect of the vaccine on reducing colonisation is possible.

More studies of the mechanisms of vaccine efficacy on airway bacteria and exacerbation phenotypes are now needed. In future bacterial vaccine studies, patients with COPD need to be selected for the presence of significant airway bacterial colonisation, for chronic bronchitis that is also associated with airway bacteria,[10] together with exacerbation risk. This will need larger vaccine studies, and we know from the COVID-19 vaccine experience that large numbers of patients can be recruited into vaccine studies. The bacterial vaccine used in this study is easy to administer and safe and would benefit

from the incorporation of a pneumococcal vaccine. There are so few targets for exacerbation prevention in COPD that further consideration of this vaccine is required, especially if it can potentially impact hospital admissions in our patients with more severe COPD.

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