ARN National Institute for Health and Care Excellence

Health Technology Evaluation

Dupilumab for treating moderate to severe chronic obstructive pulmonary disease ID6235

Response to stakeholder organisation comments on the draft remit and draft scope

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Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Sanofi	It is both timely and appropriate to refer this topic to NICE for technology appraisal. COPD is a debilitating disease associated with a high clinical, humanistic and economic burden, driven by airflow obstruction severity, symptom burden, and the frequency and severity of exacerbations. Despite treatment with triple (or dual) inhaled therapy, a substantial proportion of patients with COPD continue to experience moderate and severe exacerbations which have significant impact on their lives and those around them. [Whittaker, 2022] It is important to recognise that current exacerbations are predictive of future exacerbations, increased deterioration of lung function and mortality – COPD is a progressive disease. Hospital readmissions soon after an exacerbation are common among patients with COPD. [Harries, 2017] In general, exacerbations are associated with most of the healthcare costs of treating COPD.	Comment noted

Section	Stakeholder	Comments [sic]	Action
		There are currently no licenced or reimbursed biologic medicines available for the treatment of COPD meaning there is a high unmet need for a targeted, effective, and well-tolerated treatment that can provide significant clinical improvements in terms of exacerbation reduction, lung function, quality of life and symptoms in patients with uncontrolled COPD despite triple therapy. This is particularly the case for patients with type 2 inflammation characterised by raised eosinophils who experience the greatest burden and worst prognosis. The efficacy and positive risk benefit ratio of dupilumab for the treatment of COPD in these patients was established in two pivotal phase III randomised controlled clinical trials (BOREAS and NOTUS). [Bhatt, 2023; Bhatt, 2024]. Bhatt et al. N Engl J Med 2023;389:205-14. Bhatt et al. N Engl J Med. 2024; DOI: 10.1056/NEJMoa2401304. Harries et al. NPJ Prim Care Respir Med. 2017;27(1):31. **Whittaker et al. International Journal of Chronic Obstructive Pulmonary Disease. 2022 Volume 17: 427-437.**	
	AstraZeneca UK Ltd	AstraZeneca consider the proposed evaluation route to be appropriate.	Comment noted
	Association of Respiratory Nurses	Where do you consider dupilumab will fit into the existing care pathway for COPD? Maybe useful to comment on why very severe cohort excluded from biologic. After triple inhaled therapy is initiated and people with COPD continue to have an impacted QoL due to symptom burden and the number of antibiotic / oral corticosteroid/ number of exacerbations • SABA use	Comment noted. Technologies are appraised within their marketing authorisations.

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		• Inhaler adherence • COPD Assessment Test (CAT) is a questionnaire • MRC • Smoking cessation, pulmonary rehabilitation offered/ attended (or tech enabled alternative), pneumococcal and influenza vaccinations, personalised self-management plan and optimising treatment for co-morbidities, e.g. cardiovascular disease should also be considered as recommended outcomes in the biologic care pathway. • Access and referral to a virtual ward/tech enabled long term monitoring if available. Last line of first paragraph, include very severe FEV1 parameter. Less than 30%. Comments later re FEV1 and ratio,	
	British Thoracic Society	Highly appropriate and timely	Comment noted
	Asthma + Lung UK	A single technology appraisal is appropriate.	Comment noted
Wording	Sanofi	The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion on the 30th May 2024 recommending the approval of dupilumab in the European Union (EU) as an add-on maintenance treatment in adults with uncontrolled chronic obstructive pulmonary disease (COPD) characterized by raised blood eosinophils on a combination of an inhaled corticosteroid (ICS), a long-acting beta2agonist	Thank you for your comment. As the marketing authorisation is currently unconfirmed, it is more appropriate to keep the

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		(LABA), and a long-acting muscarinic antagonist (LAMA), or on a combination of a LABA and a LAMA if ICS is not appropriate. [EMA, 2024] This is still subject to change until the final marketing authorisation (MA) is granted. The European Commission is expected to announce a final decision on the Dupixent application in the coming months. An application has been made on the [redacted] to the MHRA for a UK MA extension to the existing dupilumab licence. The MHRA licence submission wording, aligned with CHMP for dupilumab for the treatment of COPD is: [redacted] The patient population to be considered in our base case submission is based on patients included in the Phase III clinical trials BOREAS and NOTUS. These studies included patients with raised blood eosinophils, optimised on dual or triple inhalers but who remained uncontrolled. We suggest that to avoid confusion and to fully represent the expected licence population the wording of the population in the remit should be adjusted to: *Adults with COPD and raised eosinophils who are uncontrolled on triple inhaled therapy or dual therapy where ICS is not appropriate.*	remit broad and aligned with publicly available information in the clinical trial.

Section	Stakeholder	Comments [sic]	Action
		EMA/CHMP/146624/2024 https://www.ema.europa.eu/en/documents/smop/chmp-post-authorisation-summary-positive-opinion-dupixent_en.pdf	
	AstraZeneca UK Ltd	The appropriate patient population for this appraisal are patients with moderate-to-severe chronic obstructive pulmonary disease (COPD) with type 2 inflammation, with high exacerbation risk despite being on triple inhaled therapy, that is, a long-acting muscarinic antagonist (LAMA) in combination with a long-acting beta-2 agonist (LABA) and an inhaled corticosteroid (ICS), or on dual inhaled therapy, that is, LABA in combination with a LAMA, if ICS was contraindicated. Type 2 inflammation in this regard should be defined as patients with blood eosinophils ≥300 cells/microliter, as per BOREAS/NOTUS inclusion criteria. High exacerbation risk should be defined as exacerbation history of ≥2 moderate or ≥1 severe within the last year, as per BOREAS/NOTUS inclusion criteria. The wording of the remit should reflect the population to be appraised, in line with the pivotal trials BOREAS/NOTUS. AstraZeneca, therefore, kindly request the wording to be updated accordingly.	Thank you for your comment. As the marketing authorisation is currently unconfirmed, it is more appropriate to keep the remit broad and aligned with publicly available information in the clinical trial.
	Association of Respiratory Nurses	Please add ‘can’ cause breathing difficulties (line 2). (line 4) ‘persistent’ rather than consistent.	Comment noted. Some amendments to the background section have been made. The

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		(line 5) add 'often' progressive breathlessness. 3rd paragraph – (1st line) Treatment for COPD aims to slow its progression and control the symptoms, add 'and prevent/reduce exacerbations'. (line 5) add/change (that is people who have 1 severe or 2 moderate exacerbations within a year, rather than, people who have severe disease. (line7) add or inhaled corticosteroids (ICS) 'if has asthmatic features or features suggesting steroid responsiveness. Last line, also recommends smoking cessation and pulmonary rehabilitation, add 'pneumococcal and influenza vaccinations, personalised self-management plan and optimising treatment for co-morbidities, e.g. cardiovascular disease.'	background section aims to provide a brief summary of the disease and how it is managed and is not designed to be exhaustive.
	Asthma + Lung UK	Yes	Comment noted
Additional comments on the draft remit	Sanofi	None	Comment noted
	AstraZeneca UK Ltd	N/A	Comment noted
	Primary Care Respiratory Society – UK (PCRS-UK)	Primary Care Respiratory Society urges NICE to include a primary care perspective in technology appraisal. We would welcome the introduction of biologics to a wider cohort of patients with modifiable traits, to include those with moderate to severe COPD, who might have improved clinical outcomes with targeted treatment. However, in assessing clinical and cost effectiveness, there are various primary care considerations which will be relevant to more widespread use of biological in this group which would have cost and service implications, and are essential to appraise as part of this evaluation; 1. How patients who might benefit for dupilumab will be identified	Comment noted

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		Most patients with COPD are diagnosed and cared for entirely in primary care. Identification suitable patients by identifying relevant treatable traits will require regular assessment and access to diagnostic testing e.g. blood eosinophils, FeNO along with clear guidance on how to interpret this and refer on. This would be difficult to achieve currently without increased investment in the primary are workforce, relevant diagnostic testing and guidance for identification/referral. 2. Referral pathways and eligibility criteria To prevent secondary care services from being overwhelmed there is a real need to ensure primary care is appropriately resourced to be able to effectively manage those who can be supported in the community and only refer those who may benefit from these novel treatments with clear pathways based on the type of patients that would be suitable for this type of treatment.	
	Asthma + Lung UK	n/a	Comment noted

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Sanofi	The background information supplied in the draft scope is generally accurate. However, we believe that the impact of exacerbations on outcomes should be highlighted. This is important for an understanding of the condition and for the goals of treatment for people with COPD. There is a rapid decline in health status and lung function following severe exacerbations, and hospital readmission rates (more exacerbations) and mortality are high in the weeks after every severe exacerbation. [Suissa,	Comment noted. The background section of the scope aims to provide a brief summary of the disease and how it is managed and is not

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		2012]. Exacerbations (and exacerbations compounding future exacerbations) have been identified as a key factor in COPD progression within the GOLD framework. Therefore, the prevention and treatment of severe exacerbations is an important goal in the long term management of COPD. We request that the background description in the draft scope is supplemented with the following two key points to reflect the importance of exacerbations: • *Exacerbations are predictive of further exacerbations*. For example, data from the UK CPRD HES linkage shows that increasing number and severity of exacerbations are associated with increasing risk of subsequent exacerbations [Whittaker, 2022] • *Exacerbations are a risk factor for mortality: T*he same UK data source indicates that exacerbations of COPD are associated with increased all-cause and COPD-related mortality. [Whittaker, 2024] Suissa et al. Thorax 2012;67:957–963 Whittaker et al. International Journal of Chronic Obstructive Pulmonary Disease 2022; 17: 427-437 Whittaker et al. Thorax 2024; 79:202–208	designed to be exhaustive.

	AstraZeneca UK Ltd	AstraZeneca suggests the following addition to the background information presented within the draft scope:
		• Expansion on the unmet need, including:
		  ○ COPD-related morbidity
		  ○ Number of patients continuing to exacerbate despite maximal inhaled therapy (including rescue OCS use)
			Comment noted. The background section of the scope aims to provide a brief summary of the disease and how it is managed and is not

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			designed to be exhaustive.
	Chiesi Limited	Chiesi would like to highlight that the referenced COPD prevalence figures are UK estimates which should be updated to reflect current estimates in England. The proportion/number of these patients who would be eligible for treatment with dupilumab should be indicated under 'background information'. Following the summary of NICE guideline NG115, further detail of the Dupilumab eligible COPD cohort should be provided, including specification of Type 2 inflammation in COPD.	Comment noted and brief detail on type 2 inflammation has been added. The background section of the scope aims to provide a brief summary of the disease and how it is managed and is not designed to be exhaustive.
	Association of Respiratory Nurses	NICE COPD states ratio of below 0.7 (70%) is consistent with diagnosis of COPD (alongside clinical symptoms) This document states ratio below 70% or FEV1 below 80% FEV1 is not used to determine obstruction, it is used for determining severity Having the comment re FEV1 in this document may cause confusion regarding the results of objective measurements "Moderate COPD is defined as FEV_1 between 50-79% predicted normal and severe COPD is defined as FEV_1 between 30-49**%** predicted normal." Why use mepolizumab as a comparator when it's not licensed, and it failed to reach its primary outcomes in COPD trials to date as far as aware?	Comment noted. Amendments to reflect guidance in NG115 have been made. The included comparator list is purposely broad, due to the marketing authorisation wording being unconfirmed. The committee will consider the appropriate comparators based on the available evidence and confirmed marketing authorisation.

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	British Thoracic Society	A substantial proportion of patients with COPD continue to exacerbate despite inhaled triple therapy (LAMA/LABA.ICS). Exacerbations are responsible for the majority of cost associated with COPD (approximately 60%) and is the cause of the vast majority of hospital readmissions in COPD. Exacerbations of COPD are one of the largest causes of medical emergency hospital admissions and the highest cause of hospital readmission. We would suggest that the focus of the background around treatment focuses on exacerbations. There are a number of therapies that improve breathlessness and exercise capacity and essential for stable COPD management (e.g. pulmonary rehabilitation, lung volume reduction) but do not have major impact on exacerbations, which is where this appraisal will lie. Roflumilast is rarely used clinically (discussed below).	Comment noted. The background section of the scope aims to provide a brief summary of the disease and how it is managed and is not designed to be exhaustive.
	Asthma + Lung UK	Accurate and complete	Comment noted
Population	Sanofi	To avoid confusion and be in line with our suggested update to the remit, we propose that the population is defined in line with the licence as: 'Adults with COPD and raised eosinophils who are uncontrolled on triple inhaled therapy or dual therapy where ICS is not appropriate'	Thank you for your comment. The wording has been updated in line with the trial population: 'Adults with moderate to severe COPD and raised eosinophils who have uncontrolled disease on triple inhaled therapy or

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			dual therapy where ICS is not appropriate'.
	AstraZeneca UK Ltd	The appropriate patient population for this appraisal are patients with moderate-to-severe chronic obstructive pulmonary disease (COPD) with type 2 inflammation, with high exacerbation risk despite being on triple inhaled therapy, that is, a long-acting muscarinic antagonist (LAMA) in combination with a long-acting beta-2 agonist (LABA) and an inhaled corticosteroid (ICS), or on dual inhaled therapy, that is, LABA in combination with a LAMA, if ICS was contraindicated. Type 2 inflammation in this regard should be defined as patients with blood eosinophils ≥300 cells/microliter, as per BOREAS/NOTUS inclusion criteria. High exacerbation risk should be defined as exacerbation history of ≥2 moderate or ≥1 severe within the last year, as per BOREAS/NOTUS inclusion criteria. The wording should reflect the population to be appraised, in line with the pivotal trials BOREAS/NOTUS. AstraZeneca, therefore, kindly request the wording to be updated accordingly	Thank you for your comment. The population has been updated: 'Adults with moderate to severe COPD and raised eosinophils who have uncontrolled disease on triple inhaled therapy or dual therapy where ICS is not appropriate'. The wording is purposely broad, due to the marketing authorisation wording being unconfirmed. The committee will consider the appropriate population based on the available evidence and confirmed marketing authorisation.
	Chiesi Limited	The population should align with the trial population - Adults aged 40 to 80 with moderate-to-severe COPD with Type 2 inflammation and high exacerbation risk, as an add-on to maintenance treatment with triple therapy	Thank you for your comment. The population has been updated: 'Adults with

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		(ICS/LABA/LAMA) or double therapy (LABA/LAMA) if inhaled corticosteroids is contraindicated. Type 2 inflammation should be defined as an absolute blood eosinophil count of at least 300 microlitres in order to align with the trial population. We also question whether it would be relevant to also consider the population eligible for Dupilumab only after a trial of a PDE4 inhibitor given the significant cost and administration differences between PDE4 inhibitors and biologics.	moderate to severe COPD and raised eosinophils who have uncontrolled disease on triple inhaled therapy or dual therapy where ICS is not appropriate'. The wording is purposely broad, due to the marketing authorisation wording being unconfirmed. The committee will consider the appropriate population based on the available evidence and confirmed marketing authorisation.
	Association of Respiratory Nurses	Age needs to be defined.	Thank you for your comment. The wording is purposely broad, due to the marketing authorisation wording being unconfirmed. The committee will consider the appropriate population based on the available evidence and confirmed marketing

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			authorisation. No change to scope required
	British Thoracic Society	We would suggest that the population is those that continue to exacerbate despite triple inhaled therapy. “Type 2 inflammation” will need to be defined. This is likely to be those with a blood eosinophil count of ≥300 (or $0.3x10^9$)	Thank you for your comment. The population has been updated: ‘Adults with moderate to severe COPD and raised eosinophils who have uncontrolled disease on triple inhaled therapy or dual therapy where ICS is not appropriate’. The wording is purposely broad, due to the marketing authorisation wording being unconfirmed. The committee will consider the appropriate population based on the available evidence and confirmed marketing authorisation
	Asthma + Lung UK	A clinical definition of moderate and severe COPD is included (‘FEV1 less than 79% predicted normal and severe COPD is defined as FEV1 less than 50% predicted normal.’) and is correct.	Thank you for your comment. The population has been

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		And whilst moderate and severe COPD based on FEV1 is clear, other severity factors from trial population will need to be considered around eligibility – the appropriate threshold level of eosinophil count, breathlessness, quality of life, symptom scores (e.g. CAT score) as well as exacerbation frequency, hospitalisation history and the presence of other medical problems.	updated: 'Adults with moderate to severe COPD and raised eosinophils who have uncontrolled disease on triple inhaled therapy or dual therapy where ICS is not appropriate'. The wording is purposely broad, due to the marketing authorisation wording being unconfirmed. The committee will consider the appropriate population based on the available evidence and confirmed marketing authorisation
Subgroups	Sanofi	Dupilumab specifically inhibits Type 2 (T2) inflammation. T2 inflammation in respiratory diseases including COPD, is associated with higher mortality, increased risk of exacerbations, lower FEV_1 and higher health status impairment. [Bhatt, 2023]. A subset of around 40% of COPD patients have evidence of T2 inflammation. These patients can be characterised by raised blood eosinophils (eos) counts and were the patients included in the two PhIII studies NOTUS and BOREAS. (Blood eos ≥300 cells per microlitre). Consequently '*raised blood eosinophils'* appears in the expected licence wording.	Comment noted. Population updated to include raised blood eosinophils, and the following subgroups have been included: • High eos (≥500 cells per microlitre)

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		Fractional exhaled nitric oxide (FeNO) is also a demonstrated biomarker of T2 inflammation in respiratory diseases and can additionally be used to identify COPD patients with a T2 inflammatory phenotype. Data from the dupilumab COPD trial program indicates that a subset of patients with very high eos (≥500 cells per microlitre) and/or high FeNO (≥20 ppb) may have improved outcomes in terms of exacerbation reduction and FEV_1 improvement. Therefore, we suggest that two subgroups could be considered separately to include patients with: • High eos (≥500 cells per microlitre) • High FeNO (≥20 ppb) Bhatt et al. N Engl J Med 2023;389:205-14.	• High FeNO (≥20 ppb)
	AstraZeneca UK Ltd	N/A	Comment noted
	Chiesi Limited	Type 2 inflammation, with an absolute blood eosinophil count of at least 300 microlitres should be considered as a subgroup of COPD expected to be more clinically and cost effective than the whole COPD population. This is also in line with the trial population.	Comment noted. No action required. Population updated to include raised blood eosinophils
	Association of Respiratory Nurses	Do we need to consider those with preserved or supra high lung volumes (and normal FEV1/FVC ratio) and confirmed pulmonary emphysema on CT on this pathway. Consider Consider Z-Score / LLN with preserved ratio.	Comment noted. No action required.

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		What about PRIsm?	
	British Thoracic Society	Dupilumab is expected to be more cost-effective in COPD patients with evidence of type 2 inflammation and the trials are only in this sub-population	Comment noted
	Asthma + Lung UK	Patients with comorbidities; and what comorbidities may exclude someone. Patients who still smoke. Patients who exacerbate very frequently and/or have frequent hospitalisation	Comment noted. No action required.
Comparators	Sanofi	Currently treatment in UK clinical practice for people with COPD consists of a combination of an inhaled corticosteroid (ICS), a long-acting beta2-agonist (LABA), and a long-acting muscarinic antagonist (LAMA), or a combination of a LABA and a LAMA if ICS is not appropriate. The phIII clinical trials BOREAS and NOTUS included dual or triple therapy as appropriate, in the placebo arm which is aligned to UK clinical practice. The dupilumab arm included dupilumab treatment as add-on to dual/triple inhaled therapy, as above. Therefore, a within-trial comparison is most suitable for the base case analysis. Neither roflumilast nor mepolizumab are relevant comparators for this appraisal because they cannot be considered current standard care in the UK. **Roflumilast**	Comment noted. The comparators are kept inclusive. The comparators have been updated to include standard care without dupilumab, roflumilast and azithromycin.

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		Roflumilast use is highly limited in the UK clinical setting (we estimate this to be around 0.5% of the NICE TA461 eligible population). We have sought advice about the suitability of roflumilast as a comparator in this appraisal from a number of clinicians and nurses. They were adamant that roflumilast cannot be considered standard care in the UK because it is very rarely used in clinical practice for the following reasons: ***-Clinical efficacy*****,** Roflumilast did not meet the prespecified primary end point of reduction in moderate or severe exacerbations in the phIII clinical trials REACT and RE^{2}SPOND [Martinez, 2015; Martinez, 2016] ***-High discontinuation rate.*** In the clinical trials there was an increased incidence of GI-associated adverse events (AEs) and a higher discontinuation rate (>25%). [Martinez, 2015; Martinez; 2016]. An even higher rate in AEs has been observed in the real world, aligned with the clinical opinion we received. [Cill, 2019; Munos, 2015; Park, 2019; Salvesen, 2018; Gómez, 2017; Albrecht, 2024]. An indirect treatment comparison between roflumilast and dupilumab would be highly uncertain. This is because there is limited overlap between the roflumilast and dupilumab clinical trial populations for the following reasons: 1. There was variable maintenance inhaler requirement for inclusion in the roflumilast studies. Whereas there was a requirement for maintenance triple inhaler therapy in the dupilumab studies (unless ICS was not tolerated). 2. The roflumilast NICE TA recommendation was made in a subgroup of clinical trial populations with severe COPD (FEV1 30% to <50% predicted). The dupilumab studies included patients with moderate and severe COPD (FEV1 30% to <70% predicted).	

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		3. There is no published analysis of patients with T2 inflammation from the roflumilast studies. Whereas in the dupilumab studies all patients had evidence of T2 inflammation (blood eos ≥300 cells per microlitre). Additionally, the potential improvement in both HRQoL and symptoms with roflumilast as add-on to triple therapy was not assessed in the two pivotal trials [Martinez, 2015; Martinez, 2016]. NICE TA461 relied on literature values for the quality of life health states included in the modelling. This means that no HRQoL data collected directly in patients treated with roflumilast is available for comparison with the trial HRQoL data available for dupilumab treated patients. **Mepolizumab** Mepolizumab is not a valid comparator because it is not licensed for the treatment of patients with COPD and therefore remains an investigational product. Although it appears in the NICE work program [GID-TA10239] it carries no recommendation in this therapy area and is not used in the UK in standard clinical practice. There is currently no published mepolizumab data from the latest phIII study with which to carry out an appropriate indirect comparison with dupilumab treated patients. There are no other relevant comparators. Cilli et al. 2019. J Thorac Dis. 2019; 11(4): 1100–1105 Gómez-Rodríguez M et al. Eur J Intern Med 2017;43:e28-9 Albrecht 2024 ATS, 2024 Abstract	

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		Martinez et al. Lancet 2015; 385(9971): 857-866. Martinez et al. Am J Respir Crit Care Med 2016;194(5): 559-567. Muñoz-Esquerre M et al. Pulm Pharmacol Ther. 2015 ;30:16-21 Park et al. Int J Chron Obstruct Pulmon Dis. 2019; 14: 871–879 Salvesen et al. Basic & Clinical Pharmacology & Toxicology 2018; 123.3: 314-319	
	AstraZeneca UK Ltd	AstraZeneca consider the comparators to be appropriate and an exhaustive list.	Comment noted. The comparators are kept inclusive. The comparators have been updated to include standard care without dupilumab, roflumilast and azithromycin.
	Chiesi Limited	Mepolizumab is not currently licenced for COPD and should only be considered if it currently forms part of standard of care. Chiesi agrees that Roflumilast is a relevant comparator. Given the upcoming UK pipeline of inhaled PDE4 inhibitors which will be available in an inhaled formulation, and therefore expected to be associated with an improved safety profile – it is important to consider the population eligible for Dupilumab only after a trial of a PDE4 inhibitor given the significant cost and administration differences between PDE4 inhibitors and biologics.	Comment noted. The comparators are kept inclusive. The comparators have been updated to include standard care without dupilumab, roflumilast and azithromycin.

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	British Thoracic Society	While dual bronchodilator therapy (LABA/LAMA) could be used as a comparator, this may not be needed as all patients with type 2 inflammation and exacerbations would be expected to be on an inhaled cortico-steroid, and probably triple inhaled therapy (ICS/LAMA/LABA). In the trials of dupilumab fewer than 2% of patients were on dual therapy (intolerant of ICS) While the NICE technology appraisal (TA461) concluded that roflumilast as an option for add-on to triple therapy, the drug is rarely used in UK clinical practice. The clinical experience of respiratory physicians in the UK is that it is poorly tolerated due to side effects, and has insufficient efficacy. Mepolizumab assessment is still awaited, pending phase 3 trials. Macrolide therapy (azithrymycin) is more commonly used as an off label treatment to reduce exacerbations. This also has a number of side effects and duration of therapy is unknown. It may be more effective in non type 2 inflammation. However, as it is commonly used as add on therapy for exacerbations would be a more appropriate comparison than roflumilast.	Comment noted. The comparators are kept inclusive. The comparators have been updated to include standard care without dupilumab, roflumilast and azithromycin.
	Asthma + Lung UK	The comparators listed are relevant, but treatments for frequent exacerbations in COPD are smoking cessation, triple inhaled therapy, physiotherapy including OPEP devices and regular azithromycin should also be considered.	Comment noted. The comparators have been updated to include standard care without dupilumab, roflumilast and azithromycin.

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Outcomes	Sanofi	The outcomes listed are appropriate.	Comment noted
	AstraZeneca UK Ltd	AstraZeneca consider the outcomes to be appropriate.	Comment noted
	Chiesi Limited	Moderate to severe exacerbations should be considered as these are considered clinically significant	Comment noted. The list of outcomes is not exhaustive, therefore data on outcomes could be submitted, if available.
	Association of Respiratory Nurses	Might be worth also adding MACE/ 'major cardiovascular events incidence' as an outcome measure. Evidence shows that patients with COPD have higher risk of having a stroke or/and MI particularly post exacerbation. Consider health resource, anxiety/depression, exercise capacity/physical activity, self-efficacy as outcomes?.	Comment noted. The list of outcomes is not exhaustive, therefore data on outcomes could be submitted, if available.
	British Thoracic Society	Exacerbations, both moderate and severe, are the primary outcome of interest. Hospitalisation should also be considered.	Comment noted. The list of outcomes is not exhaustive, therefore data on outcomes could be submitted, if available.
Equality	Sanofi	COPD is a debilitating disease that disproportionately affects people from lower socioeconomic groups and with specific demographics and protected characteristics such as ethnicity and age.	Comment noted. We have noted your comment in the equality impact form (EIA). This

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		Based on data for 2022/23 published by Public Health England, people from the poorest 10% of households were 1.7 times more likely to develop COPD than people from the most affluent 10% of households.[PHE, 2023] Higher levels of social deprivation have also been associated with an increased risk of exacerbations among patients with COPD in the UK. [Williams, 2022]. In England between March 2021 and January 2023, age-standardised mortality rates due to COPD were highest in the most deprived areas, among people who had never worked or were in long-term unemployment, and men of Bangladeshi background. Age-standardised mortality rates due to COPD were consistently higher in men than in women across all regions in England. [ONS, 2023]. Disparities in care for patients with COPD linked to ethnicity and socioeconomic status have also been noted in England. In a 2011 audit of chronic disease management in London, black patients were less likely to be prescribed pharmacological treatments including SABAs, SAMAs, LAMAs and ICS + LABA than patients of white background, while patients with south Asian heritage were less likely to receive LAMAs than white patients. Black and south Asian patients were also less likely to be referred for COPD pulmonary rehabilitation than patients of White background. [Martin, 2012]. COPD patients are less mobile and often unable to access care, as evidenced by the disparity in pulmonary rehab. [Francis, 2023] Dupilumab will be delivered via HomeCare directly to patients' homes which may help to address access barriers especially outside urban centres where further geographical challenges exist. It is important for the committee to consider the disproportionate impact of COPD on these disadvantaged groups and how the provision of a targeted,	will be considered by the committee.

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		effective, and well-tolerated treatment could improve their health and reduce inequalities. Martin et al. Br J Gen Pract. 2012;62(595):e76-81. Francis A and Cumella A 2023, Unmet need and barriers in provision of pulmonary rehabilitation for people with COPD: findings from a large UK survey , BTS 2023 Office for National Statistics (ONS). Inequalities in mortality involving common physical health conditions, England: 21 March 2021 to 31 January 2023. 2023. PHE. Office for Health Improvement and Disparities. Public health profiles by deprivation deciles 2024. https://fingertips.phe.org.uk. Williams y. BMJ Open Respir Res. 2022;9(1).	
	AstraZeneca UK Ltd	N/A	Comment noted
	Association of Respiratory Nurses	Patients who have been diagnosed with COPD based on Z-Score / LLN instead of fixed 0.7 (70%) ratio. Generally speaking, younger patients are frequently underdiagnosed with COPD using the fixed 0.7 (70%) ratio – if this is used as a criterion for dupilumab, it could rule out many younger patients who would otherwise be eligible for the add-on maintenance therapy.	Comment noted. We have noted your comment in the equality impact form (EIA). This will be considered by the committee.
	British Thoracic Society	COPD is a disease that predominately affects people from socio-economic deprived background and multiple long-term conditions. Socio-economic deprivation is a major risk factor for exacerbations and need for hospital care. New therapies that reduce exacerbations may therefore help reduce inequality, but it would be needed that access is possible. Also, people from deprived backgrounds are more likely to continue to smoke, and this would need to be considered as if people who continue to smoke despite	Comment noted. We have noted your comment in the equality impact form (EIA). This will be considered by the committee.

Section	Consultee/ Commentator	Comments [sic]	Action
		being offered smoking cessation were excluded this could indirectly discriminate against those from deprived backgrounds.	
	Asthma + Lung UK	It does not appear that this draft remit and scope could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed. By defining eligibility by the need for basic COPD care to have been optimised, access to the drug will depend on this being available. We know that basic care is very poorly delivered in COPD (to less than 20% of patients). This includes the availability of a quality assured spirometry test. Whilst this is essential to diagnose COPD, we know these tests are not available everywhere, and are not always performed to the required level of accuracy. Some locations will be unable to provide this test, or have long waiting lists, which will mean delays for certain populations to accessing drug simply due to their postcode. This requirement may also be limiting to those without the physical ability to do a spirometry test. The use of CT scanning is likely to be useful in assessing for comorbidities such as lung cancer and bronchiectasis, but again access to these tests may be a limiting factor in access to the drug as well as the consequences of having a comorbidity that will impact suitability for dupilamab.	Comment noted. No action required.
Other considerations	Sanofi	Dupilumab represents a significant innovation in the management of COPD and so should be considered a step change in this therapy area for the following reasons:	Thank you for your comment.

Section	Consultee/ Commentator	Comments [sic]	Action
		• Dupilumab will be the first biologic to be licenced for the treatment of COPD. • It specifically targets T2 inflammation in a well-defined group of COPD patients. • This systemic mode of action contrasts with the current best available therapy which comprises inhalers (with oral steroid treatment for acute exacerbations). These do not specifically target the underlying cause of the T2 inflammation. • Systemic corticosteroids are often used in COPD and have multiple undesirable side effects which are particularly relevant for the susceptible population of patients with COPD. Similarly, antibiotics are frequently used for the treatment of respiratory infection in COPD patients and also have undesirable side effects such as Clostridium difficil infection, possible antimicrobial resistance and gastrointestinal upset. A statistically significant reduction versus placebo was observed in both steroid and antibiotic use in the dupilumab COPD phIII studies. • Treatment adherence to inhalers and poor inhaler technique are significant issues in the management of COPD leading to poor outcomes. [Lerodiakonou 2020; Turégano-Yedro 2023]. Dupilumab differs from SoC because it is an injectable medicine given every two weeks. Whilst outcomes for the COPD indication have not yet been observed in the real world clinical setting; compliance and persistence rates for patients with asthma or atopic dermatitis on dupilumab are high (For example. [redacted]).	

Section	Consultee/ Commentator	Comments [sic]	Action
		• Patients with COPD have a high degree of disease related morbidity and impaired functioning including the ability to walk short distances or in some cases even leave their homes. Dupilumab is delivered by homecare which is expected to be a significant benefit to patients and may be a factor in adherence and persistence on treatment. In the clinical trial programme dupilumab is the first biologic to show significant improvement versus standard care in all of the core COPD outcomes including: exacerbation reduction, lung function, symptom control and quality of life. In addition, it is indicated in several T2 co-morbidities (see section below for licenced indications) frequently observed in patients with COPD. Lerodiakonou et al. BMC Pulmonary Medicine 2020 20:253 **Turégano-Yedro et al. Int. J. COPD 2023:18 2887–2893**	
	AstraZeneca UK Ltd	N/A	Comment noted.
	Chiesi Limited	Consideration should be given to the method of administration of Dupilumab (sub-cutaneous injection) compared to the other comparators listed, including those in development, and the challenges this may pose for patient use.	Comment noted. No change to the scope required.
	Asthma + Lung UK	n/a	Comment noted.
Questions for consultation	Sanofi	N/A	Comment noted.
	AstraZeneca UK Ltd	**Where do you consider dupilumab will fit into the existing care pathway for COPD?**	Comments noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		Dupilumab is likely to be an add-on to maintenance treatment, i.e. triple therapy or dual therapy if ICS is contra-indicated. Do you consider that the use of dupilumab can result in any potential substantial health-related **benefits that are unlikely to be included in the QALY calculation?** N/A **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** N/A	
	Chiesi Limited	<u>Where do you consider dupilumab will fit into the existing care pathway for COPD?</u> It is estimated that 60 – 80% of COPD patients do not present with evidence of Type 2 inflammation[1] and the study population for Dupilumab is limited to patients with Type 2 inflammation. In contrast, PDE4 inhibitors are not restricted to use in the Type 2 inflammation cohort. As such, under the current care pathway, Roflumilast (an oral PDE4 inhibitor) can be used in combination with ICS/LABA/LAMA (for people who had 2 or more exacerbations in the previous 12 months despite triple inhaled therapy). There is also an upcoming UK pipeline of inhaled PDE4 inhibitors for which ongoing phase III studies support their positioning as an add-on to triple therapy for exacerbating patients.[2, 3] These products will be available in an inhaled formulation, and therefore expected to be associated with an improved safety profile.	Comments noted. No action required.

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		We therefore propose that exacerbating patients on triple therapy should receive PDE4 inhibitors as an add-on treatment prior to Dupilumab initiation due to the more complex method of administration (sub-cutaneous injection vs inhaled/oral route), likely higher cost and the anticipated need to involve secondary and tertiary care specialists in at least the first prescription of biologic agents, for Dupilumab compared with PDE4 inhibitors. [1] Bhatt et al., 2023. Dupilumab for COPD with type 2 inflammation indicated by eosinophil counts. New England Journal of Medicine, 389(3), pp.205-214. [2] PILLAR study, NCT04636814 Study Details | A 52-week, Placebo- and Active- Controlled (Roflumilast, Daliresp® 500µg) Study to Evaluate the Efficacy and Safety of Two Doses of CHF6001 DPI (Tanimilast) as add-on to Maintenance Triple Therapy in Subjects With COPD and Chronic Bronchitis. (PILLAR) | ClinicalTrials.gov [3] PILASTER study, NCT04636801 Study Details | A 52-week, Placebo-controlled Study to Evaluate the Efficacy and Safety of 2 Doses of CHF6001 DPI (Tanimilast), as add-on to Maintenance Triple Therapy in Subjects With COPD and Chronic Bronchitis (PILASTER) | ClinicalTrials.gov Are the comparators listed the only relevant comparators? As mentioned in response to the 'Comparators' section above - Chiesi agrees that Roflumilast is a relevant comparator. Chiesi would also like to highlight that given the upcoming UK pipeline of inhaled PDE4 inhibitors which will be available in an inhaled formulation, and therefore expected to be associated with an improved safety profile – it is important to consider the population eligible for Dupilumab only after a trial of a PDE4 inhibitor given the significant cost and administration differences between PDE4 inhibitors and biologics.	
	Association of Respiratory Nurses	Has there been patient and public involvement?	Comments noted. No action required.

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	Asthma + Lung UK	**Where do you consider dupilumab will fit into the existing care pathway for COPD?** We need some understanding of the volume of patients who may qualify for assessment for dupilamab – this will require a pathway that covers primary care identification and referral, an assessment in secondary or tertiary care, and mechanism for drug initiation/delivery. In secondary care is likely the most suitable place for this pathway to sit, potentially utilising a hub and spoke model - dupilumab could be prescribed out of secondary care but delivered in a community setting for accessibility to patients. But capacity in secondary care must be considered - most of these cases do not currently leave primary care, and this new, additional work for secondary care will need an increase in workload and therefore resource. It is essential that the pathway for accessing dupilumab is not limited by only being available via tertiary care – as we have seen in the delivery of severe asthma biologics, this can create long delays between referral and drug initiation due to tertiary centre capacity, and geographical disparities in patients being able to access these centres. **Do you consider that the use of dupilumab can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** Use of oral corticosteroids could be reduced by dupilimab and therefore the impact of associated side effects of oral corticosteroids should be considered such as osteoporosis prevention and treatment, diabetes costs in those that develop it, weight gain, mental health effects etc.	Comments noted. No action required.

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Additional comments on the draft scope	Sanofi	None	Comment noted.
	AstraZeneca UK Ltd	N/A	Comment noted.
	Chiesi Limited	Economic Analysis: COPD is lifelong and without a cure. The time horizon should be a lifetime horizon to ensure the economic analysis is sufficiently long enough to capture any differences in costs and outcomes.	Comment noted.
	Asthma + Lung UK	• System readiness must be considered and how this may impact the uptake, and therefore outcome of this drug entering the market. The drug has the potential to have an impact in the moderate/severe COPD population with frequent exacerbations and the appropriate pattern of inflammation, and thus help a currently underserved population. It cannot replace the NICE 5 Fundamentals of COPD Care which we know aren't being delivered to most patients. • However the availability of this drug could help drive improvements in basic care as clinicians will have to have put people through them before they are eligible but only if this treatment is reserved for patients with optimised care i.e. a correct diagnosis confirmed by quality assured spirometry, comorbidities addressed, stopped smoking, had all vaccinations, completed pulmonary rehabilitation and are adherent with the correct inhaler technique to their inhaled therapies. The health system will need to increase throughput to these services or risk giving non-optimised patients expensive drugs or marking them unsuitable for biologics incorrectly. • Patient identification must also be considered (e.g. tool like SPECTRA): there will be a significant number of incorrectly diagnosed patients i.e. not COPD or have been diagnosed with inadequate spirometry who will need a full work up by specialist care, however it is now unusual to do	

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		monitoring spirometry on COPD patients. This should be considered alongside the many thousands of people who could qualify for dupilumab and would need referring. This is a significant cost for the NHS, both from a systems and drug cost perspective, even before new clinics are created and staffed and including new capacity for spirometry. These patients will also need following up by specialist clinics. • Lessons to be learned from severe asthma biologics (See Consensus pathway for managing uncontrolled asthma in adults)	

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

GSK
Novartis UK