Supplementary Materials

Biologic Therapies in COPD: The Development Pipeline and the Unresolved Problem of Patient Selection

Manuscript ID biomedicines-4662531

Table S1. Sources searched, the search strings as executed, and the selection flow.

S1a. Sources and what was run in each.

Source	What was searched	Yield
Embase (Elsevier), 1974 to present, embase.com	#1 'chronic obstructive lung disease'/exp/mj OR 'lung emphysema'/exp/mj OR 'chronic bronchitis'/exp/mj OR copd:ti,ab,kw OR 'chronic obstructive pulmonary disease':ti,ab,kw OR emphysema:ti,ab,kw OR 'chronic bronchitis':ti,ab,kw #2 mepolizumab:ti,ab,kw OR benralizumab:ti,ab,kw OR depemokimab:ti,ab,kw OR dupilumab:ti,ab,kw OR itepekimab:ti,ab,kw OR tozorakimab:ti,ab,kw OR astegolimab:ti,ab,kw OR tezepelumab:ti,ab,kw OR ecleralimab:ti,ab,kw OR solrikitug:ti,ab,kw OR lunsekimig:ti,ab,kw OR felcorekibart:ti,ab,kw OR infliximab:ti,ab,kw OR etanercept:ti,ab,kw OR canakinumab:ti,ab,kw OR biologic*:ti,ab,kw OR 'monoclonal antibody':ti,ab,kw #3 'interleukin 5':ti,ab,kw OR 'interleukin 5 receptor':ti,ab,kw OR 'interleukin 4 receptor':ti,ab,kw OR 'interleukin 13':ti,ab,kw OR 'interleukin 33':ti,ab,kw OR st2:ti,ab,kw OR il1rl1:ti,ab,kw OR 'thymic stromal lymphopoietin':ti,ab,kw OR tslp:ti,ab,kw OR cxcr2:ti,ab,kw OR 'tumor necrosis factor alpha':ti,ab,kw OR 'interleukin 1beta':ti,ab,kw OR 'phosphatidylinositol 3 kinase delta':ti,ab,kw #4 #1 AND (#2 OR #3) AND [2019-2026]/py	1,036 records exported on 12 October 2026
Scopus (Elsevier)	TITLE-ABS-KEY ((copd OR “chronic obstructive pulmonary disease” OR “chronic obstructive lung disease” OR emphysema OR “chronic bronchitis”) AND (mepolizumab OR benralizumab OR depemokimab OR dupilumab OR itepekimab OR tozorakimab OR astegolimab OR tezepelumab OR ecleralimab OR solrikitug OR lunsekimig OR felcorekibart OR infliximab OR etanercept OR canakinumab OR biologic* OR “monoclonal antibody” OR interleukin* OR alarmin* OR “thymic stromal lymphopoietin” OR tslp OR st2 OR il1rl1 OR cxcr2 OR “tumor necrosis factor” OR “tumour necrosis factor” OR pi3k)) AND PUBYEAR > 2018 AND PUBYEAR < 2027	2,233 records exported on 12 September 2026
ClinicalTrials.gov (API v2)	Condition COPD combined with each named agent and each molecular target, restricted to interventional studies of phase 2 or above.	Census of 36 studies, closed 30 September 2026, provided as a separate data package
Terms tested and not retained	The Emtree class terms 'biological therapy'/exp and 'monoclonal antibody'/exp were tested and then removed: exploding them retrieved a predominantly oncological literature and raised the yield to approximately 12,000 records without adding relevant ones. The class concept was therefore carried by free text only. In Scopus the mechanism block is deliberately broader (interleukin*, alarmin*) because truncation on class terms over-matched.	—

Both strings were re-verified against the exported record sets: every record in both exports concerns COPD, emphysema or chronic bronchitis (1,036/1,036 and 2,232/2,233), and the publication years span 2019 to 2026 with no record outside that interval, which confirms the condition block and the year limit as written. Of the exported records, 3.4% (Embase) and 1.3% (Scopus) are not matched by any of the terms above in the exported title, abstract and keyword fields; these were retrieved through indexing terms held in the full database record.

S1b. The three term groups, combined with the Boolean operator AND.

Group	Terms	Notes
Group (i) — the condition	COPD; chronic obstructive pulmonary disease; emphysema; chronic bronchitis	controlled vocabulary and free text
Group (ii) — named agents	mepolizumab; benralizumab; depemokimab; dupilumab; itepekimab; tozorakimab; astegolimab; tezepelumab; ecleralimab; solrikitug; lunsekimig; felcorekibart; infliximab; etanercept; canakinumab	with free-text terms for the agent class
Group (iii) — molecular targets	interleukin-5 and its receptor; interleukin-4 receptor alpha; interleukin-13; interleukin-33; ST2 and IL1RL1; thymic stromal lymphopoietin; CXCR2; tumour necrosis factor alpha; interleukin-1 beta; phosphoinositide 3-kinase delta	combined with group (i) by AND

S1c. Selection flow.

Step	n	Notes
Records entering deduplication	3,256	1,033 from Embase and 2,223 from Scopus
Duplicate records removed	631	matched on DOI, then on PMID, then on normalised title
Unique records	2,625	allocated to three pools
Pool A1 — core pharmacological literature	894	screened against the eligibility criteria
Pool A2 — mechanistic periphery	1,317	retained as background; not screened for inclusion
Pool B — grey literature	414	conference abstracts and preprints; consulted only where no peer-reviewed source existed
Pool A1 excluded on title and abstract	586	against the prespecified criteria, applied by a single reviewer
Pool A1 retained for full reading	308	
Excluded on reading	44	asthma-COPD overlap 21 (an editorial decision by the authors, stated in Section 2); off topic 12; not in English 8; cost and accessibility only 2; preclinical 1
Final set informing the review	264	by section: patient selection and biomarkers 66; framing, guidelines and stability 63; target biology 45; pivotal trials and secondary analyses 44; pipeline and agents in development 20; real-world evidence 19; lessons from failure 4; endpoint methodology 3

Counts are taken from the exported search files and the screening workbooks. The difference between the number of records exported and the number entering deduplication is accounted for by records whose exported bibliographic metadata could not be parsed. Screening was carried out by a single reviewer (P.-V.M.), which is stated as a limitation in Section 2.

Table S2. Self-assessment of this review against the six SANRA items.

SANRA item	How it is addressed	Where
1. Justification of the article's importance for the readership	Addressed in the Introduction, which sets out the density of the 2024-2026 period, the arrival of the first agents effective without eosinophil selection, and the GOLD 2026 position.	Section 1
2. Statement of concrete aims or formulation of questions	Three questions are stated explicitly at the end of the Introduction, and the Introduction now names where each is answered.	Section 1; answered in Sections 3, 4 and 5-7
3. Description of the literature search	Sources, term groups, date of the final search, registry census date, screening procedure, priority rules, the handling of trials without a primary publication, and the stated limitations of single-reviewer screening and of the absence of risk-of-bias assessment.	Section 2; Table S1
4. Referencing	Every claim that rests on a specific result carries a citation to the primary source; registry records are cited where no primary publication exists, and conference abstracts and	Throughout; References 1-69

SANRA item	How it is addressed	Where
	sponsor announcements are identified as such in the text.	
5. Scientific reasoning	Effect estimates are given with confidence intervals; subgroup analyses are identified as such and are not presented as evidence of effect modification; the distinction between prognostic and predictive biomarkers, and between clinical stability and disease modification, is maintained explicitly.	Sections 3, 5, 6.1-6.4, 7.3
6. Appropriate presentation of data	Trial-level data are tabulated with eligibility criteria and results (Table 1), ongoing programmes with the question each addresses (Table 2), and the state of the evidence on selection with the corresponding unmet needs (Table 3). Figures 1 and 2 present the pathways with their agents and candidate selection biomarkers, and the chronology of the pipeline.	Tables 1-3; Figures 1 and 2

SANRA is a scale for the quality assessment of narrative reviews rather than a reporting guideline; the manuscript therefore states that it is reported with reference to SANRA. This table records how each item has been addressed so that the correspondence can be checked item by item.