NATIONALE VERSORGUNGS LEITLINIEN

Nationale VersorgungsLeitlinie

Asthma

Recherchedokumentation + Evidenztabellen

Version 5

AWMF-Register-Nr. nvl-002

Träger:

Bundesärztekammer

Kassenärztliche Bundesvereinigung

Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften

Inhaltsverzeichnis

1 Recherchedokumentation

1.1 Themenübergreifende strukturierte Recherche nach systematischen Übersichtsarbeiten

1.1.1 PICO-Fragestellung

Es wurden systematische Übersichtsarbeiten zum Thema „Asthma“ gesucht, die als primäre Evidenzquellen für die Aktualisierung der NVL Asthma dienen sollen.

- Population: Asthma
- Intervention: keine Einschränkung; für Aktualisierung (Version 5) insbesondere aus den Themenbereichen Medikamentöse Therapie bei Erwachsenen und Kindern, digitale Gesundheitsanwendungen*
- Vergleich: keine Einschränkung
- Endpunkte: Mortalität, Lebensqualität, Erwerbs(un-)fähigkeit, Asthmakontrolle (Symptome, Asthmaexazerbationen), Unerwünschte Wirkungen
- Studientyp: systematische Übersichtsarbeiten
- Suchzeitraum: ab November 2018 (Ende Suchzeitraum systematische Recherche für 4. Auflage der NVL Asthma).

*Entsprechend der priorisierten Themen für den vorrangigen Aktualisierungsbedarf.

Recherchequellen

Als Quellen für die themenübergreifende strukturierte Suche nach hochwertigen systematischen Übersichtsarbeiten wurden folgende Institutionenen aufgrund ihrer evidenzbasierten Vorgehensweise, ihrer hohen Berichtsqualität, ihrer wissenschaftlichen Unabhängigkeit, eines weitergehenden Einblicks in Studiendossiers sowie ggf. ihres Bezugs zum deutschen bzw. europäischen Versorgungskontext ausgewählt:

- Cochrane
- AHRQ (Agency for Healthcare Research and Quality)
- NICE (National Institute for Health and Care Excellence)
- IQWiG (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen)

Ein- und Ausschlusskriterien

Einschluss	**E**	Einschluss: Fragestellung passend, Studientyp passend
	Ep	noch nicht veröffentlicht (Protokoll, Berichtsplan o. Ä. vorhanden)
	Ez	zurückgestellt für iteratives Vorgehen (z.B. Detailfragestellung)
Ausschluss	Aa	thematisch nicht passend: andere Erkrankung/ Fragestellung/Thema
	Ap	Studientyp nicht passend
	Aq	Methodische Qualität
	Ad	Doppelpublikation / bereits in 4. Auflage inkludiert
	As	Sprache nicht deutsch oder englisch
	Ap	Publikationstyp (z.B. Protokoll, thematisch nicht passend)
	Aw	zurückgezogen

1.1.2 Recherchestrategien

Die Recherchestrategien (z. B. Datenbanksuche, Schlagwortsuche, einfaches Screening) richteten sich nach den Möglichkeiten der jeweiligen Recherchequelle.

Cochrane Library (05.10.2022)

Nr.	Suchfrage	Anzahl
#4	#1 OR #2 in Cochrane Protocols; Publication date from 2018-11-01	8

Nr.	Suchfrage	Anzahl
#3	#1 OR #2 in Cochrane Reviews; Publication date from 2018-11-01	47
#2	(Asthma*):ti,ab,kw (Word variations have been searched)	36390
#1	MeSH descriptor: [Asthma] explode all trees	12270

IQWiG (15.09.2022)

Nr.	Suchfrage
Suchbegriffe	Asthma (https://www.iqwig.de/projekte/projekte-und-ergebnisse/#searchQuery=query=Asthma&page=1&rows=10&sortBy=score&sortOrder=desc&facet.filter.language=de)
Filter	Projekte und Ergebnisse
Suchzeitraum	13.11.2018 – 15.09.2022
Treffer	9
Treffer nach Titelscreening	7 ▪ **Dupilumab (Kinder & Jugendliche)** https://www.iqwig.de/projekte/a22-46.html (beide Berichtsdokumente: Kurzfassung der Nutzenbewertung; Dossierbewertung) ▪ **Dupilumab 2019 (Jugendliche und Erwachsene)** https://www.iqwig.de/projekte/a19-74.html (beide Berichtsdokumente: Kurzfassung der Nutzenbewertung; Dossierbewertung) ▪ **Mepolizumab (Kinder ab 6J.)** https://www.iqwig.de/projekte/a18-58.html (beide Berichtsdokumente: Kurzfassung der Nutzenbewertung; Dossierbewertung) ▪ **Beclometason/Formoterol/Glycopyrronium** https://www.iqwig.de/projekte/a21-18.html (beide Berichtsdokumente: Kurzfassung der Nutzenbewertung; Dossierbewertung) ▪ **Beclometason/Formoterol/Glycopyrronium (Asthma) - Addendum** https://www.iqwig.de/projekte/a21-85.html (Berichtsdokument: Addendum) ▪ **Indacaterolacetat / Glycopyrroniumbromid / Mometasonfuroat (Asthma)** https://www.iqwig.de/projekte/a20-69.html (beide Berichtsdokumente: Kurzfassung der Nutzenbewertung; Dossierbewertung) ▪ **Indacaterolacetat / Glycopyrroniumbromid / Mometasonfuroat (Asthma)-Addendum** https://www.iqwig.de/projekte/a20-125.html (Berichtsdokument: Addendum)

NICE (16.09.2022)

Nr.	Suchfrage
Suchbegriffe	Asthma auf Startseite
Filter	Keine
Suchzeitraum	Publiziert nach dem 13.11.2018
Treffer	80 + zusätzlich 8 (in development)
Treffer nach Titelscreening	4 (davon n = 1 “in development”) ▪ **Dupilumab** www.nice.org.uk/guidance/ta751 ▪ **Mepolizumab** (Erwachsene) www.nice.org.uk/guidance/ta671 ▪ **Benralizumab** (Erwachsene) www.nice.org.uk/guidance/ta565 ▪ **Tezepelumab** (in development; Stand 28.11.2022) www.nice.org.uk/guidance/indevelopment/gid-ta10796

AHRQ (15.09.2022)

Nr.	Suchfrage
Suchbegriffe	Asthma in EPC Evidence-based reports
Suchzeitraum	13.11.2018 – 15.09.2022
Filter	-
Treffer	2
Treffer nach Titelscreening	0

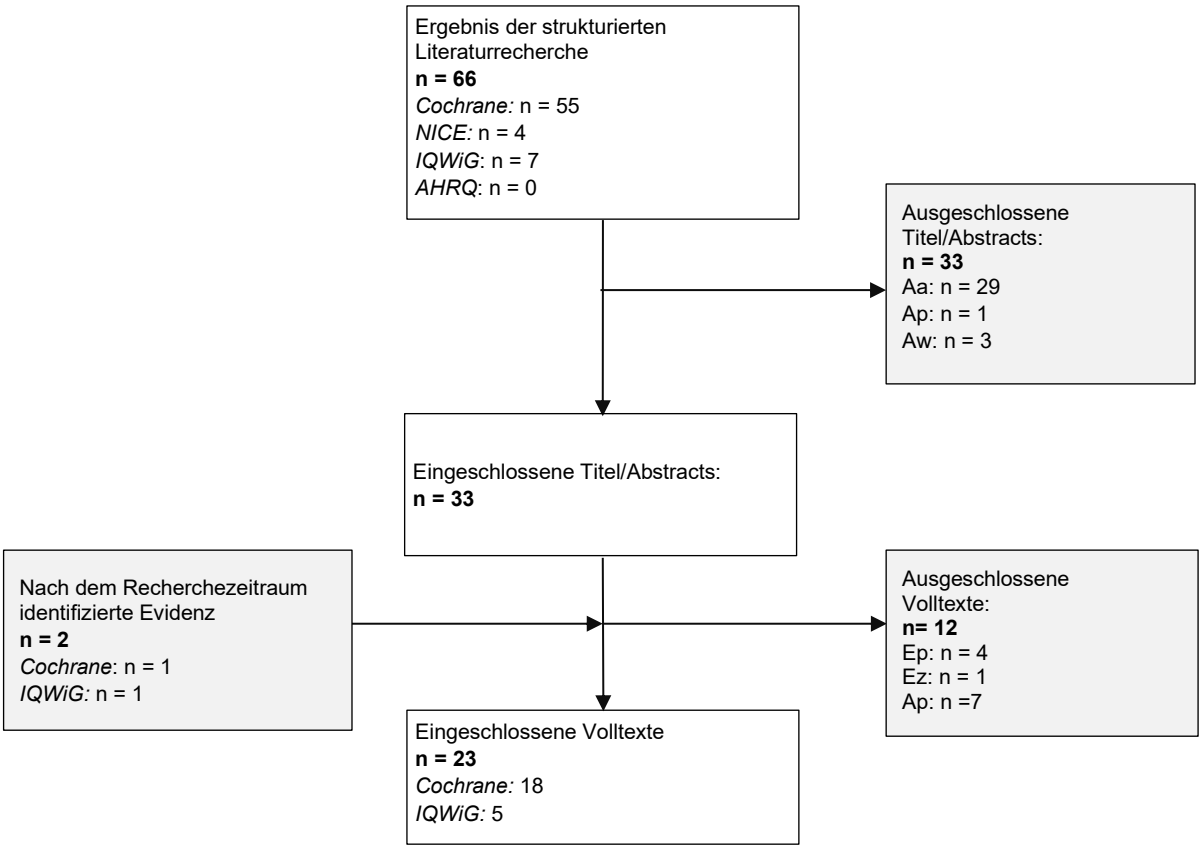
Nach dem Recherchezeitraum:

- Wurde die Aktualisierung eines Cochrane-Reviews zu Vitamin D [1] sowie
- die Nutzenbewertung vom G-BA zu Tezepelumab [2] veröffentlicht.

Beide Publikationen wurden in die NVL Asthma inkludiert.

Neu eingeschlossene Treffer insgesamt nach Ausschlüssen: n=18 Cochrane-Reviews, n=5 Nutzenbewertungen des G-BA.

1.1.3 Flowchart



1.2 Fixkombination als Bedarfstherapie in Stufe 1 und 2

1.2.1 Vorüberlegungen

In der vorab durchgeführten themenübergreifenden strukturierten Recherche wurde ein Cochrane Review identifiziert, welcher sowohl nach einer bedarfsorientierten Anwendung der Fixkombination aus SABA/ICS, als auch nach der Fixkombination aus ICS und Formoterol bei Erwachsenen und Kindern mit mildem Asthma gesucht hat (Crossingham 05/2021: Combination fixed-dose beta agonist and steroid inhaler as required for adults or children with mild asthma, https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013518.pub2/full).

Bedarfsweise SABA/ICS Fixkombination: Die SABA Albuterol und Terbutalin waren in der Suchstrategie des Cochrane Reviews aufgeführt, daher wurde eine Update-Recherche hierzu nach Ende des Suchzeitraumes dieses Reviews durchgeführt. Da Fenetorol nicht in dessen Recherchestrategie inkludiert war, wurde dieser Wirkstoff separat und ohne Eingrenzung des Suchzeitraumes als Bestandteil der Fixkombination gesucht.

Bedarfsweise Fixkombination aus Formoterol und ICS: Für diese Fixkombination wurde zusätzlich eine Update Recherche der für die 4. Auflage der NVL Asthma durchgeführten systematischen Recherche zum Thema umgesetzt (letzte Suche: 30.04.2019).

1.2.2 PICO-Fragestellung: bedarfsweise Fixkombination SABA/ICS

Population	Patient*innen mit Asthma (mild: Stufe 1 oder 2); Kinder und Erwachsene
Intervention	ausschließlich bedarfsweise Fixkombination aus ICS und einem SABA in Stufe 1 und 2
Comparison	Standardtherapie
Outcome	Mortalität, Lebensqualität, Erwerbs(un-)fähigkeit, Asthmakontrolle (Symptome, Asthmaexazerbationen), Unerwünschte Wirkungen
Studientyp	RCT: iteratives Vorgehen: Phase-III-Studien abwärts

1.2.3 Recherchestrategien

Grundlage für die Recherche bildet der in einer strukturierten Suche identifizierte Cochrane Review von Crossingham et al. (2021). Da Fenetorol nicht in dessen Recherchestrategie inkludiert war, wurde dieser Wirkstoff separat und ohne Eingrenzung des Suchzeitraumes gesucht.

Medline via Pubmed (www.pubmed.gov) (08. November 2022)

Nr.	Suchfrage	Anzahl
#19	**Search: #18 NOT #15**	**21**
#18	Search: #17 AND #13	21
#17	Search: #1 AND #5 AND #16	75
#16	Search: Fenoterol[tiab]	1,583
#15	**Search: #12 AND #13 Filters: from 2021/3/1 - 3000/12/12**	**60**
#14	Search: #12 AND #13	1,414
#13	Search: randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR "clinical trials as topic" [MeSH Terms:noexp] OR randomly [tiab] OR trial [ti]	1,496,425
#12	Search: #1 AND #11	3,219
#11	Search: #9 OR #10	4,781
#10	Search: "albuterol, beclomethasone drug combinations" [Supplementary Concept]	5
#9	Search: #5 AND #8	4,781
#8	Search: #6 OR #7	23,157
#7	Search: Albuterol[tiab] OR Terbutaline[tiab] OR SABA[tiab]	7,059

Nr.	Suchfrage	Anzahl
#6	Search: "Adrenergic beta-2 Receptor Agonists"[Mesh] OR ((short-acting[tiab] OR "shortacting"[tiab]) AND adrenergic*[tiab] AND ("beta 2 Receptor Agonists"[tiab] OR "beta2-Agonists"[tiab] OR "beta-2 Agonists"[tiab])) OR "Adrenergic beta-2 Receptor Agonists" [Pharmacological Action]	20,593
#5	Search: #2 OR #3 OR #4	228,854
#4	Search: ICS[tiab] OR Beclomethasone[tiab] OR Budesonide[tiab] OR Ciclesonide[tiab] OR Fluticasone[tiab] OR Mometasone[tiab]	22,224
#3	Search: glucocorticoids[MeSH Terms] OR glucocorticoids[Pharmacological Action]	205,040
#2	Search: inhal*[tiab] AND (corticosteroid*[tiab] OR steroid*[tiab] OR glucocorticoid*[tiab] OR glucocorticosteroid*[tiab])	18,607
#1	Search: asthma[mesh] OR asthma*[tiab]	196,696

Datenbanken der Cochrane Library (08. November 2022)

Nr.	Suchfrage	Anzahl
#15	**(#3 AND #7 AND #14) not "conference abstract":pt in Trials**	**37**
#14	(Fenoterol):ti,ab,kw (Word variations have been searched)	843
#13	**(#3 AND #12) not "conference abstract":pt in Trials; Year first published from 2021**	**73**
#12	#7 AND #11	2050
#11	#8 OR #9 OR #10	6174
#10	((Albuterol or Terbutaline or SABA)):ti,ab,kw (Word variations have been searched)	5835
#9	(((short-acting or "shortacting") and adrenergic* and ("beta 2 Receptor Agonists" or "beta2-Agonists" or "beta-2 Agonists"))):ti,ab,kw (Word variations have been searched)	172
#8	MeSH descriptor: [Adrenergic beta-2 Receptor Agonists] explode all trees	485
#7	#4 OR #5 OR #6	26768
#6	((ICS or Beclomethasone or Budesonide or Ciclesonide or Fluticasone or Mometasone)):ti,ab,kw (Word variations have been searched)	19505
#5	(((inhal* and (corticosteroid* or steroid* or glucocorticoid* or glucocorticosteroid*)))):ti,ab,kw (Word variations have been searched)	8725
#4	MeSH descriptor: [Glucocorticoids] explode all trees	4825
#3	#1 OR #2	34163
#2	MeSH descriptor: [Asthma] explode all trees	12294
#1	(Asthma):ti,ab,kw (Word variations have been searched)	34156

Übersicht der eingeschlossenen Treffer

	Medline	Cochrane	Summe
RCTs	81	110	**191**

Anzahl der ausgeschlossenen Publikationen nach Ausschlussgrund:

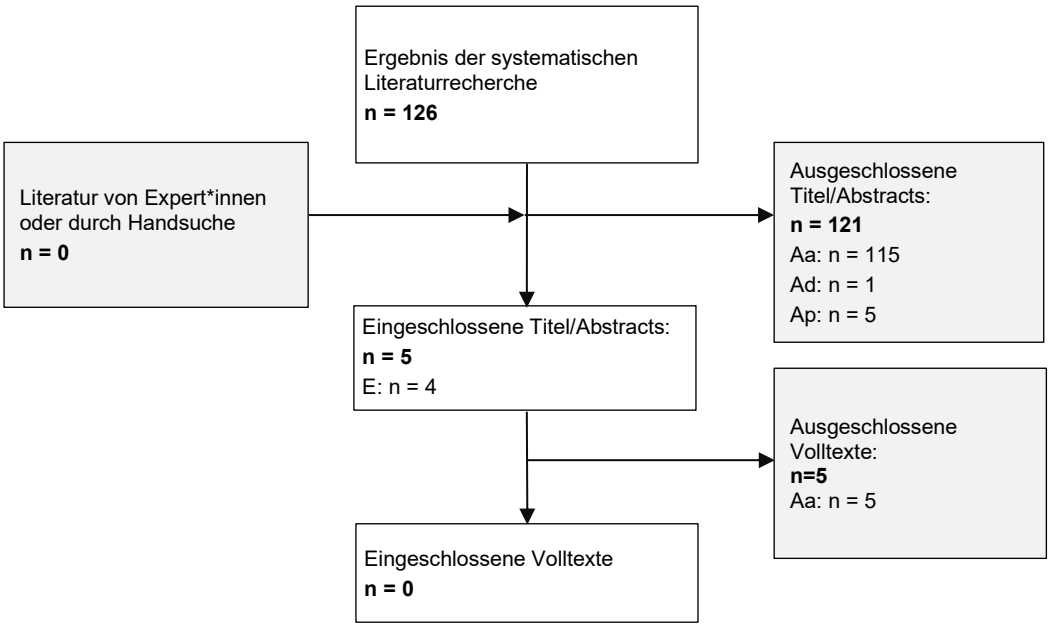
A1 (Dubletten): 39

A2 (nicht englisch/deutsch): 11

A3 (Conference Abstracts): 15

Eingeschlossene Treffer insgesamt nach Ausschlüssen: 126

1.2.4 Flowchart



1.2.5 PICO-Fragestellung: bedarfsweise Fixkombination Formoterol/ICS

Population	Patient*innen mit Asthma (mild: Stufe 1 oder 2); Kinder und Erwachsene
Intervention	ausschließlich bedarfsweise Fixkombination aus ICS und Formoterol in Stufe 1 und 2
Comparison	Standardtherapie
Outcome	Mortalität, Lebensqualität, Erwerbs(un-)fähigkeit, Asthmakontrolle (Symptome, Asthmaexazerbationen), Unerwünschte Wirkungen
Studientyp	RCT: iteratives Vorgehen: Phase-III-Studien abwärts

1.2.6 Recherchestrategien

Update der systematischen Recherche zum Thema. Letzte Suche: 30.04.2019.

Medline via Pubmed (www.pubmed.gov) (17. November 2022)

Nr.	Suchfrage	Anzahl
#13	**Search: #10 AND #11 Filters: from 2019/4/30 - 3000/12/12**	**73**
#12	Search: #10 AND #11	544
#11	Search: randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR "clinical trials as topic" [MeSH Terms:noexp] OR randomly [tiab] OR trial [ti]	1,498,172
#10	Search: #1 AND #9	1,212
#9	Search: #7 OR #8	1,692
#8	Search: (("fluticasone-formoterol" [Supplementary Concept]) OR "Budesonide, Formoterol Fumarate Drug Combination"[Mesh]) OR "Mometasone Furoate, Formoterol Fumarate Drug Combination"[Mesh]	253
#7	Search: #5 AND #6	1,678
#6	Search: formoterol[tiab] OR "Formoterol Fumarate"[Mesh]	2,886
#5	Search: #2 OR #3 OR #4	228,974
#4	Search: ICS[tiab] OR Beclomethasone[tiab] OR Budesonide[tiab] OR Ciclesonide[tiab] OR Fluticasone[tiab] OR Mometasone[tiab]	22,257

Nr.	Suchfrage	Anzahl
#3	Search: glucocorticoids[MeSH Terms] OR glucocorticoids[Pharmacological Action]	205,119
#2	Search: inhal*[tiab] AND (corticosteroid*[tiab] OR steroid*[tiab] OR glucocorticoid*[tiab] OR glucocorticosteroid*[tiab])	18,624
#1	Search: asthma[mesh] OR asthma*[tiab]	196,854

Datenbanken der Cochrane Library (17. November 2022)

Nr.	Suchfrage	Anzahl
#15	**(#3 AND #14) not "conference abstract":pt in Trials; Year first published: from 2019**	**182**
#14	#11 OR #12 OR #13	2334
#13	MeSH descriptor: [Budesonide, Formoterol Fumarate Drug Combination] explode all trees	228
#12	MeSH descriptor: [Mometasone Furoate, Formoterol Fumarate Drug Combination] explode all trees	7
#11	#7 AND #10	2334
#10	#8 OR #9	3436
#9	(formoterol):ti,ab,kw (Word variations have been searched)	3436
#8	MeSH descriptor: [Formoterol Fumarate] explode all trees	1203
#7	#4 OR #5 OR #6	26767
#6	((ICS or Beclomethasone or Budesonide or Ciclesonide or Fluticasone or Mometasone)):ti,ab,kw (Word variations have been searched)	19504
#5	(((inhal* and (corticosteroid* or steroid* or glucocorticoid* or glucocorticosteroid*)))):ti,ab,kw (Word variations have been searched)	8725
#4	MeSH descriptor: [Glucocorticoids] explode all trees	4825
#3	#1 OR #2	34163
#2	MeSH descriptor: [Asthma] explode all trees	12294
#1	(Asthma):ti,ab,kw	34156

Übersicht der eingeschlossenen Treffer

	Medline	Cochrane	Summe
RCTs	73	182	**255**

Anzahl der ausgeschlossenen Publikationen nach Ausschlussgrund:

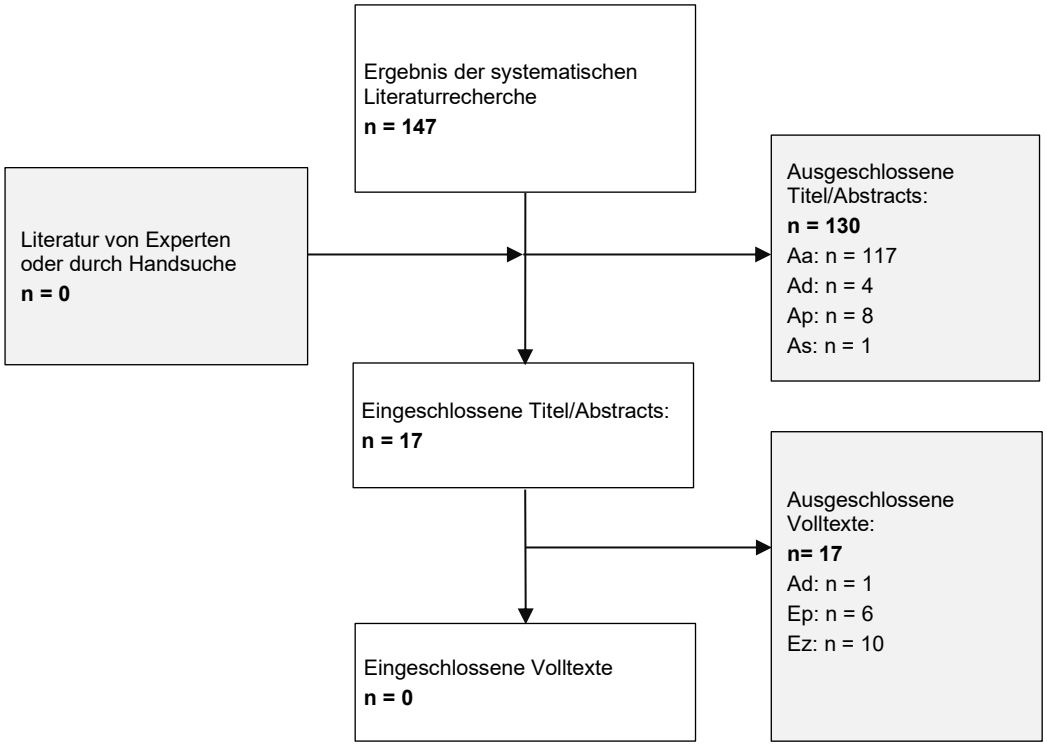
A1 (Dubletten): 53

A2 (nicht englisch/deutsch): 4

A3 (Conference Abstracts): 51

Eingeschlossene Treffer insgesamt nach Ausschlüssen: 147

1.2.7 Flowchart



1.3 Dreifach-Fixkombination (LAMA/LABA/ICS)

1.3.1 PICO-Fragestellung

Population	Patient*innen mit Asthma (ab Stufe 4)
Intervention	Fixkombination aus LAMA/LABA/ICS
Comparison	Standardtherapie
Outcome	Mortalität, Lebensqualität, Erwerbs(un-)fähigkeit, Asthmakontrolle (Symptome, Asthmaexazerbationen), Unerwünschte Wirkungen, zusätzlich: Adhärenzverbesserung
Studientyp	RCT: iteratives Vorgehen: Phase-III-Studien abwärts

1.3.2 Recherchestrategien

Medline via Pubmed (www.pubmed.gov) (11.03.2022)

Nr.	Suchfrage	Anzahl
#20	**Search: #18 AND #19**	**96**
#19	Search: randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR "clinical trials as topic" [MeSH Terms:noexp] OR randomly [tiab] OR trial [ti]	1,444,467
#18	Search: #3 AND #17	349
#17	Search: #8 AND #12 AND #16	1,068
#16	Search: #13 OR #14 OR #15	10,896
#15	Search: LABA[tiab]	2,027

Nr.	Suchfrage	Anzahl
#14	Search: Abediterol[tiab] OR (Clenbuterol[tiab] OR "Clenbuterol"[Mesh]) OR Carmoterol[tiab] OR Olodaterol[tiab] OR Indacaterol[tiab] OR Vilanterol[tiab] OR Bambuterol[tiab] OR Arformoterol[tiab] OR (Formoterol[tiab] OR "Formoterol Fumarate"[Mesh]) OR (Salmeterol[tiab] OR "Salmeterol Xinafoate"[Mesh])	7,926
#13	Search: "Adrenergic beta-2 Receptor Agonists"[Mesh] OR ((long-acting[tiab] OR "longacting"[tiab]) AND adrenergic*[tiab] AND ("beta 2 Receptor Agonists"[tiab] OR "beta2-Agonists"[tiab] OR "beta-2 Agonists"[tiab]))	3,358
#12	Search: #9 OR #10 OR #11	12,880
#11	Search: LAMA[tiab]	1,667
#10	Search: Darotropium[tiab] OR Umeclidinium[tiab] OR Glycopyrronium[tiab] OR Aclidinium[tiab] OR (tiotropium[tiab] OR "Tiotropium Bromide"[Mesh])	2,585
#9	Search: "Muscarinic Antagonists"[Mesh] OR ((Long-acting[tiab] OR longacting[tiab]) AND (anticholinergic*[tiab] OR anti-cholinergic*[tiab] OR antimuscarinic*[tiab] OR (Muscarinic*[tiab] AND Antagonist*[tiab])))	10,411
#8	Search: #4 OR #5 OR #6 OR #7	227,135
#7	Search: ICS[tiab]	10,219
#6	Search: Mometasone[tiab] OR Flunisolide[tiab] OR Ciclesonide OR (Triamcinolone[tiab] OR "Triamcinolone"[Mesh]) OR (Beclomethasone[tiab] OR "Beclomethasone"[Mesh]) OR (Budesonide[tiab] OR "Budesonide"[Mesh]) OR (Fluticasone[tiab] OR "Fluticasone"[Mesh])	26,962
#5	Search: glucocorticoids[MeSH Terms] OR glucocorticoids[Pharmacological Action]	201,852
#4	Search: inhal*[tiab] AND (corticosteroid*[tiab] OR steroid*[tiab] OR glucocorticoid*[tiab] OR glucocorticosteroid*[tiab])	18,053
#3	Search: #1 OR #2	191,617
#2	Search: "Asthma"[Mesh]	136,282
#1	Search: Asthma*[tiab]	171,827

Datenbanken der Cochrane Library (11.03.2022)

Nr.	Suchfrage	Anzahl
#24	**(#3 AND #23) NOT (conference abstract):pt in Trials**	**177**
#23	#8 and #15 and #22	1200
#22	#16 or #17 or #18 or #19 or #20 or #21	20576
#21	((Mometasone or Flunisolide or Ciclesonide or Triamcinolone or Beclomethasone or Budesonide or Fluticasone or ICS)):ti,ab,kw	18401
#20	MeSH descriptor: [Fluticasone] explode all trees	1810
#19	MeSH descriptor: [Budesonide] explode all trees	1910
#18	MeSH descriptor: [Beclomethasone] explode all trees	1141
#17	MeSH descriptor: [Triamcinolone Acetonide] explode all trees	1167
#16	((("inhaled corticosteroid*" or "inhaled steroid*" or "inhaled glucocorticoid*"))):ti,ab,kw (Word variations have been searched)	6346
#15	#9 or #10 or #11 or #12 or #13 or #14	8436
#14	((Abediterol or Clenbuterol or Carmoterol or Clodaterol or Indacaterol or Vilanterol or Bambuterol or Arfomoterol or Formoterol or Salmeterol or LABA)):ti,ab,kw	8238

Nr.	Suchfrage	Anzahl
#13	MeSH descriptor: [Adrenergic beta-2 Receptor Agonists] explode all trees	483
#12	MeSH descriptor: [Salmeterol Xinafoate] explode all trees	1146
#11	MeSH descriptor: [Formoterol Fumarate] explode all trees	1187
#10	MeSH descriptor: [Clenbuterol] explode all trees	49
#9	((((“beta 2 Receptor Agonists” or “beta 2 Agonists” or “beta-2 Agonists”) and (adrenergic*) and (long-acting or “longacting”)))):ti,ab,kw (Word variations have been searched)	441
#8	#4 or #5 or #6 or #7	5413
#7	(((Darotropium or Umeclidinium or Glycopyrronium or Aclidinium or Tiotropium or LAMA))):ti,ab,kw (Word variations have been searched)	4509
#6	(((Long-acting or longacting) and ((anticholinergic* or anti-cholinergic* or antimuscarinic*) or ((Antagonist* AND Muscarinic*))))):ti,ab,kw (Word variations have been searched)	1035
#5	MeSH descriptor: [Muscarinic Antagonists] explode all trees	961
#4	MeSH descriptor: [Tiotropium Bromide] explode all trees	717
#3	#1 or #2	33558
#2	MeSH descriptor: [Asthma] explode all trees	12127
#1	(Asthma):ti,ab,kw (Word variations have been searched)	33551

Übersicht der eingeschlossenen Treffer

	Medline	Cochrane	Summe
RCTs	96	177	**273**

Anzahl der ausgeschlossenen Publikationen nach Ausschlussgrund:

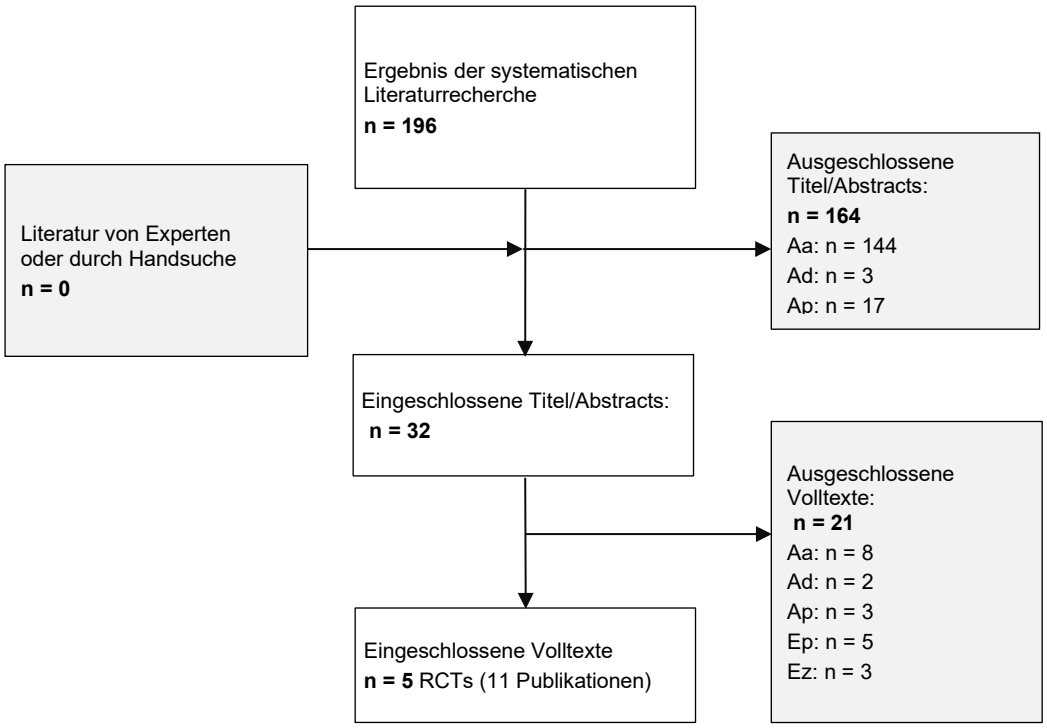
A1 (Dubletten): 62

A2 (nicht englisch/deutsch): 3

A3 (Conference Abstracts): 12

Eingeschlossene Treffer insgesamt nach Ausschlüssen: 196

1.3.3 Flowchart



1.4 Dupilumab

1.4.1 Vorüberlegungen

Der bereits für die 4. Auflage der NVL Asthma identifizierte Cochrane Review wurde aktualisiert (Gallagher A. Anti-interleukin-13 and anti-interleukin-4 agents versus placebo, antiinterleukin-5 or anti-immunoglobulin-E agents, for people with asthma. Suchdatum: 16.10.2020).

Die Zulassung für Dupilumab wurde mittlerweile erweitert (für Kinder ab 6 Jahren). Um die Wirksamkeits- und insbesondere die Sicherheitsaspekte einschätzen sowie die Stellung im Stufenschema für Kinder und Jugendliche definieren zu können – und da die Recherchen des Cochrane Reviews bzw. der NVL Asthma bereits einige Jahre her sind – wurde eine Update-Recherche durchgeführt.

1.4.2 PICO-Fragestellung

Population	Patient*innen mit Asthma; alle Altersgruppen
Intervention	Dupilumab
Comparison	jegliche Intervention
Outcome	Mortalität, Lebensqualität, Erwerbs(un-)fähigkeit, Asthmakontrolle (Symptome, Asthmaexazerbationen), Unerwünschte Wirkungen
Studientyp	RCT: iteratives Vorgehen: Phase-III-Studien abwärts

1.4.3 Recherchestrategien

Medline via Pubmed (www.pubmed.gov) (22. Mai 2023)

Nr.	Suchfrage	Anzahl
#8	**Search: #6 AND #7**	**125**
#7	Search: randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR "clinical trials as topic" [MeSH Terms:noexp] OR randomly [tiab] OR trial [ti]	1,537,167
#6	Search: #1 AND #4 Filters: from 2019/4/29 - 3000/12/12	482
#5	Search: #1 AND #4	611
#4	Search: #2 OR #3	3,121
#3	Search: anti-interleukin 4[TiAb] OR anti-IL-4[TiAb] OR anti-IL4[TiAb]	975
#2	Search: dupilumab[tiab]	2,234
#1	Search: (asthma*[tiab]) OR "Asthma"[Mesh]	200,555

Datenbanken der Cochrane Library (22. Mai 2023)

Nr.	Suchfrage	Anzahl
#7	**(#3 AND #6) NOT (Conference proceeding):pt in Trials with Publication Year from 2019 to present**	**120**
#6	#4 OR #5	924
#5	"anti-IL 4" OR "anti IL4" OR "anti-interleukin 4"	46
#4	(dupilumab):ti,ab,kw	903
#3	#1 OR #2	34813
#2	MeSH descriptor: [Asthma] explode all trees	14957
#1	(Asthma):ti,ab,kw (Word variations have been searched)	34805

Übersicht der eingeschlossenen Treffer

	Medline	Cochrane	Summe
RCTs	125	120	**245**

Anzahl der ausgeschlossenen Publikationen nach Ausschlussgrund:

A1 (Dubletten): 58

A2 (nicht englisch/deutsch): 2

A3 (Conference Abstracts): 15

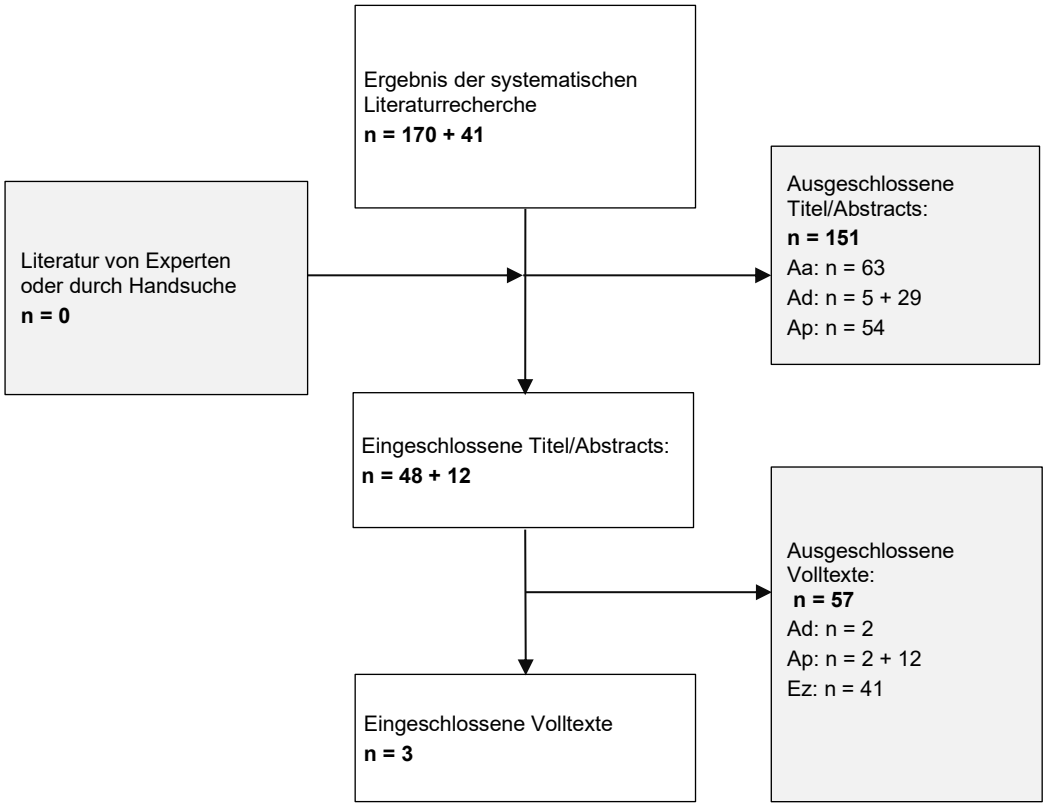
Eingeschlossene Treffer nach Ausschlüssen: 170

Clinicaltrials.gov (10. Mai 2023)

Suchfelder	Suchbegriff
Condition or disease	Asthma
Targeted search	Dupilumab
Trefferzahl (gesamt) Filters: Child (birth–17)	41 15

Eingeschlossene Treffer insgesamt: 170 + 41 (=211)

1.4.4 Flowchart



1.5 Tezepelumab

1.5.1 PICO-Fragestellung

Population	Patient*innen mit Asthma; alle Altersgruppen
Intervention	Tezepelumab
Comparison	jegliche Intervention
Outcome	Mortalität, Lebensqualität, Erwerbs(un-)fähigkeit, Asthmakontrolle (Symptome, Asthmaexazerbationen), Unerwünschte Wirkungen
Studientyp	SR; RCT: iteratives Vorgehen: Phase-III-Studien abwärts

1.5.2 Recherchestrategien

Medline via Pubmed (www.pubmed.gov) (16. Mai 2023)

Nr.	Suchfrage	Anzahl
#10	**Search: (#6 AND #8) NOT #9**	**38**
#9	**Search: #6 AND #7**	**16**
#8	Search: randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR "clinical trials as topic" [MeSH Terms:noexp] OR randomly [tiab] OR trial [ti]	1,536,140
#7	Search: (systematic review [ti] OR meta-analysis [pt] OR meta-analysis [ti] OR systematic literature review [ti] OR this systematic review [tw] OR pooling project [tw] OR (systematic review [tiab] AND review [pt]) OR meta synthesis [ti] OR meta-analy*[ti] OR integrative review [tw] OR integrative research review [tw] OR rapid review [tw] OR umbrella review [tw] OR consensus development conference [pt] OR practice guideline [pt] OR drug class reviews [ti] OR cochrane database syst rev [ta] OR acp journal club [ta] OR health technol assess [ta] OR evid rep technol assess summ [ta] OR jbi database system rev implement rep [ta]) OR (clinical guideline [tw] AND management [tw]) OR ((evidence based[ti] OR evidence-based medicine [mh] OR best practice* [ti] OR evidence synthesis [tiab]) AND (review [pt] OR diseases category[mh] OR behavior and behavior mechanisms [mh] OR therapeutics [mh] OR evaluation study[pt] OR validation study[pt] OR guideline [pt] OR pmcbook)) OR ((systematic [tw] OR systematically [tw] OR critical [tiab] OR (study selection [tw]) OR (predetermined [tw] OR inclusion [tw] AND criteri* [tw]) OR exclusion criteri* [tw] OR main outcome measures [tw] OR standard of care [tw] OR standards of care [tw]) AND (survey [tiab] OR surveys [tiab] OR overview* [tw] OR review [tiab] OR reviews [tiab] OR search* [tw] OR handsearch [tw] OR analysis [ti] OR critique [tiab] OR appraisal [tw] OR (reduction [tw]AND (risk [mh] OR risk [tw]) AND (death OR recurrence))) AND (literature [tiab] OR articles [tiab] OR publications [tiab] OR publication [tiab] OR bibliography [tiab] OR bibliographies [tiab] OR published [tiab] OR pooled data [tw] OR unpublished [tw] OR citation [tw] OR citations [tw] OR database [tiab] OR internet [tiab] OR textbooks [tiab] OR references [tw] OR scales [tw] OR papers [tw] OR datasets [tw] OR trials [tiab] OR meta-analy* [tw] OR (clinical [tiab] AND studies [tiab]) OR treatment outcome [mh] OR treatment outcome [tw] OR pmcbook)) NOT (letter [pt] OR newspaper article [pt])	650,854
#6	Search: #1 AND #5	159
#5	Search: #2 OR #3 OR #4	215
#4	Search: "tezepelumab" [Supplementary Concept]	59
#3	Search: Anti-TSLP[tiab] OR "Anti-Thymic stromal lymphopoietin"[tiab]	93
#2	Search: Tezepelumab[tiab]	140
#1	Search: asthma*[tiab] OR "Asthma"[Mesh]	200,464

Datenbanken der Cochrane Library (16. Mai 2023)

Nr.	Suchfrage	Anzahl
#9	**(#3 AND #7) NOT (conference abstract):pt in Trials**	**144**
#8	**(#3 AND #7) NOT (conference abstract):pt in Cochrane Reviews, Cochrane Protocols**	**1**
#7	#4 OR #5 OR #6	164
#6	("Anti-Thymic stromal lymphopoietin"):ti,ab,kw	10
#5	(Anti-TSLP):ti,ab,kw	24
#4	(tezepelumab):ti,ab,kw	153

Nr.	Suchfrage	Anzahl
#3	#1 OR #2	34813
#2	MeSH descriptor: [Asthma] explode all trees	14957
#1	(Asthma):ti,ab,kw (Word variations have been searched)	34805

Epistemonikos (www.epistemonikos.org) (16. Mai 2023)

Nr.	Suchfrage	Anzahl
#1	(title:(asthma* AND tezepelumab) OR abstract:(asthma* AND tezepelumab)); Publication Type: Sytematic Reviews	11

Übersicht der eingeschlossenen Treffer

	Medline	Cochrane	Epistemonikos	Summe
Aggregierte Evidenz	16	1	11	**28**
RCTs	38	144		**182**
GESAMT				**210**

Anzahl der ausgeschlossenen Publikationen nach Ausschlussgrund:

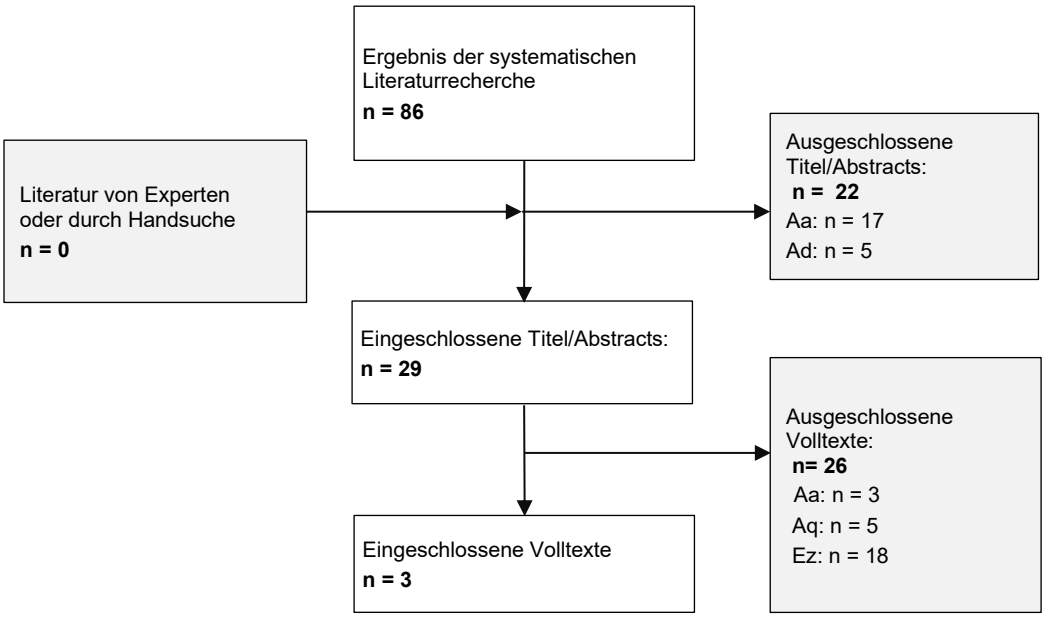
A1 (Dubletten): 35

A2 (nicht englisch/deutsch): 0

A3 (Conference Abstracts): 89

Eingeschlossene Treffer insgesamt nach Ausschlüssen: 86

1.5.3 Flowchart



2 Evidenztabellen Medikamentöse Therapie

2.1 Cochrane Reviews

2.1.1 Fixkombination als Bedarfstherapie in Stufe 1 und 2

Zitat	Charakteristika desSR	Ergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
Crossingham I. Combination fixed-dose beta agonist and steroid inhaler as required for adults or children with mild asthma. Cochrane Database Syst Rev 2021; 5(5):CD013518. https://www.ncbi.nlm.nih.gov/pubmed/33945639	**Allgemeine Angaben:** Metaanalyse, (RCTs and cross-over trials) **Fragestellung:** To evaluate the elicacy and safety of single combined (fast-onset beta2-agonist plus an inhaled corticosteroid (ICS)) inhaler only used as needed in people with mild asthma. **Suchzeitraum:** 03/ 2021 **Population:** adults or children with mild asthma (n=9657) **Intervention:** single fixed-dose FABA/ICS inhaler used as required **Control:** 1. No treatment, 2. Placebo, 3. As-required SABA, 4. Regular ICS with as-required SABA, 5. Regular fixed-dose combination ICS/LABA, with or without asrequired SABA, or 6. Regular fixed-dose combination ICS/LABA with as-required ICS/FABA **Primary Outcomes:** 1. Exacerbations requiring systemic steroids 2. Hospital admissions/emergency department or urgent care visits for asthma 3. Measures of asthma control	**<u>As-required FABA/ICS inhalers compared to as-required FABA inhalers for mild asthma</u>** >> Kommentar: Poolen sinnvoll? Studien sind NovelSTART und SYGMA1 **Asthma exacerbation requiring systemic steroid** 52/1000 vs. 109/1000; OR 0.45 (95% CI 0.34; 0.60); I^2 = 0% ; 2 RCTs, n = 2997; **GRADE: HIGH** **Hospital admission, ED and urgent care visits** 12/1000 vs. 43/1000; OR 0.35 (95% CI 0.20; 0.60); I^2 = 0%; 2 RCTs, n = 2997; **GRADE: LOW** **Asthma control (Lower scores = better control)** MD -0.15 (95% CI -0.20; -0.10); I^2 = 0% ; 2 RCTs, n = 2859; **GRADE: MODERATE** **All Adverse events** 437/1000 vs. 486/1000; OR 0.82 (95% CI 0.71; 0.95); I^2 = 0%; 2 RCTs; n = 3002; **GRADE: MODERATE** **<u>As-required FABA/ICS inhalers compared to regular inhaled steroid for mild asthma</u>** >> Kommentar: Poolen sinnvoll? Studien sind NovelSTART und SYGMA1, SYGMA2 und PRACTICAL **Asthma exacerbation requiring systemic steroid** 65/1000 vs. 81/1000; OR 0.79 (95% CI 0.59; 1.07); I^2 = 59%, 4 RCTs, n = 8065; **GRADE: LOW** **Hospital admission, ED and urgent care visits** 12/1000 vs. 19/1000; OR 0.63 (95% CI 0.44; 0.91); I^2 = 0%, 4 RCTs, n = 8065; **GRADE: LOW**	AMSTAR2: Qualität des Reviews: **- moderate** AMSTAR-Score kritische Kriterien: 7/7 erfüllt	siehe endpunktspezifische GRADE-Bewertung des Reviews	**<u>Fixkombination: Formoterol/ICS</u>** <u>(as required)</u> · 4/5 inkludierte Studien = bereits in NVL Asthma. 4. Auflage aufgeführt und diskutiert NovelSTART (4.6.1 Bedarfstherapie (alle Altersgruppen) --> 4.6.1.2 Fixkombination aus ICS niedrigdosiert und Formoterol: bedarfsorientiert in Stufe 1 SYGMA1, SYGMA2, PRACTICAL (Langzeittherapie: 4.8.1 Stufe 2 (alle Altersgruppen --> 4.8.1.2 Fixkombination aus ICS niedrigdosiert und Formoterol: bedarfsorientiert in Stufe 2) 5. Studie: Haahtela 2006: *Formoterol as needed with or without budesonide* --> wurde bereits in systematischer Recherche zur 4. Auflage zurückgestellt (Primärer EP: FeNO; Vergleichsintervention: Formoterol allein (wird nicht mehr empfohlen)) **<u>Fixkombination: SABA/ICS</u>** <u>(as required)</u> SABA wurden mit recherchiert, jedoch keine Studien im Suchzeitraum eingeschlossen Hinweis zu **Papi 2007** (Rescue use of beclomethasone and albuterol in a single inhaler for mild asthma.**):** *"Our findings are also in accord with data*

Zitat	Charakteristika desSR	Ergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
	Anzahl eingeschlossener Studien: 5 Studien; 1 Abstract	**Asthma control (Lower scores indicate better asthma control)** MD 0.12 points higher (95% CI 0.09; 0.15); I² = 0% , 4 RCTs, n = 7382; **GRADE: HIGH** **All Adverse events** 482/1000 vs. 493/1000; OR 0.96 (95% CI 0.82; 1.14); I² = 55%, 4 RCTs, n = 8072; **GRADE: MODERATE**			*from a 2007 doubleblind RCT which showed beclomethasone-salbutamol 250/100 µg in a single inhaler, administered as-required, was as elective as regular use of inhaled beclomethasone 250 µg twice daily and more elective than as-required salbutamol alone in preventing exacerbations and improving morning peak expiratory flow rate (PEFR) (Papi 2007). We judged this study to be at low risk of bias, but it was excluded from the meta-analysis because the population studied included a proportion with moderate asthma, with 31.6% receiving regular ICS, with a mean dose of **460 µg/day,** and we were unable to obtain individual patient data to determine the elects in the subgroup with mild asthma alone."*

2.1.2 Auswirkungen ICS auf das lineare Wachstum von Kindern

Zitat	Charakteristika desSR	Ergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
Axelsson I. Inhaled corticosteroids in children with persistent asthma: Effects of different drugs and delivery devices on growth. Cochrane Database Syst Rev 2019; 6(6):CD010126. https://www.ncbi.nlm.nih.gov/pubmed/31194879	**Suchzeitraum:** April 2019 **Fragestellung:** To assess the impact of different inhaled corticosteroid drugs and delivery devices on the linear growth of children with persistent asthma. **Population:** children up to 18 years of age with persistent mild-to-moderate asthma **Interventionen:** - comparison: different inhaled corticosteroid molecules at equivalent doses, delivered by the same type of device - comparison: different devices used to deliver the same inhaled corticosteroid molecule at the same dose **Outcome**: linear growth velocity **Body of Evidence**: 6 RCTs, 1199 children aged from 4 to 12 years (per-protocol population: 1008) - duration of trials varied from six to 20 months	**fluticasone vs. beclomethasone** - fluticasone given at an equivalent dose was associated with a significant greater linear growth velocity - MD 0,81 cm/y (95% KI 0,46; 1,16); 1 RCT, n = 23, Aussagesicherheit: niedrig **fluticasone vs. budesonide** - Fluticasone given at an equivalent dose had a less suppressive effect than budesonide on growth, as measured by change in height over a period from 20 weeks to 12 months - MD 0,97 cm (95% KI 0,62; 1.32); I² = 0%, 2 RCTs, n = 359, Aussagesicherheit: moderat **fluticasone vs. budesonide** - no significant di)erence in linear growth velocity between fluticasone and budesonide at equivalent doses observed - MD 0,39 cm/y (95% KI -0.94; 1.73); I² = 86,8%, 2 RCTs, n = 236, Aussagesicherheit: sehr niedrig	AMSTAR2: Qualität des Reviews: - **moderate** AMSTAR-Score kritische Kriterien: 7/7 erfüllt	siehe GRADE-Bewertungen im Ergebnisteil	

2.1.3 Kombinationstherapie aus ICS/Formoterol

Zitat	Charakteristika desSR	Ergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
Janjua S. Inhaled steroids with and without regular formoterol for asthma: Serious adverse events.	**Fragestellung:** To assess the risk of mortality and non-fatal serious adverse events (SAEs) in trials that randomly assign participants with chronic asthma to regular formoterol and inhaled corticosteroids versus the same dose of inhaled corticosteroid alone **Suchzeitraum:** 02/2019	`- ICS included beclomethasone (daily metered dosage 200 to 800 µg), budesonide (200 to 1600 µg), fluticasone (200 to 250 µg), and mometasone (200 to 800 µg) - Formoterol metered dosage ranged from 12 to 48 µg daily - Fixed combination ICS was used in most of the studies **Primary outcomes**	AMSTAR2: Qualität des Reviews: - **moderate** AMSTAR-Score kritische Kriterien: 7/7 erfüllt	siehe endpunktspezifische GRADE-Bewertung des Reviews	

Zitat	Charakteristika desSR	Ergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
Cochrane Database Syst Rev 2019; 9(9):CD006924. https://www.ncbi.nlm.nih.gov/pubmed/31553802	**Population:** adults and children with asthma of any severity **Intervention:** regular formoterol and ICS **Control:** same dose of ICS alone for at least 12 weeks **primäre Endpunkte:** • All-cause mortality • All-cause non-fatal SAEs **Body of Evidence:** - 29 studies included 35,751 adults, and 10 studies included 4035 children and adolescents - includes results from two large trials that recruited 23,422 adolescents and adults mandated by the US Food and Drug Administration (FDA)	All-cause mortality - 17/18,645 adults taking formoterol and ICS and 13/17,106 adults taking regular ICS died of any cause - 1/1000 vs. 1/1000; peto odds ratio (OR): 1,25 (95% KI 0,61; 2;56), I² = 0%, 32 RCTs, n = 35751, **moderate-certainty evidence**) - No deaths were reported in the trials on children and adolescents (10 RCTs, n= 4035, **low-certainty evidence**) All-cause non-fatal SAEs *Erwachsene* - A total of 401 adults experienced a non-fatal SAE of any cause on formoterol with ICS, compared to 369 adults who received regular ICS - 22/1000 vs. 22/1000; Peto OR; 1,00 (95% KI 0,87; 1,16); I² = 0%, 29 RCTs, n = 35751, **high-certainty evidence**) *Kinder + Jugendliche* - 30/2491 children and adolescents experienced an SAE of any cause when receiving formoterol with ICS, compared to 13/1544 children and adolescents receiving ICS alone. - 11/1000 vs. 8/1000, Peto OR: 1,33 (95% KI 0,71; 2,49); I² = 5% ,10 RCTs, n = 4035, **moderate-certainty evidence**) **Secondary outcomes (relevante)** Asthma-related mortality - no children and adolescents died from asthma, but three of 12,777 adults in the formoterol and ICS treatment group died of asthma (both low-certainty evidence) Asthma-related non-fatal SAEs *Erwachsene* - 90 adults experienced an asthma-related non-fatal SAE with formoterol and ICS, compared to 102 with ICS alone - 5/1000 vs. 6/1000 ; Peto OR: 0,86 (95% KI 0,64; 1,14); I² = 0%, 28 RCTs, n = 35158, **moderate-certainty evidence** *Kinder und Jugendliche* - Amongst children and adolescents, 9 experienced an asthma-related non-fatal SAE with formoterol and ICS, compared to 5 on ICS alone - 4/1000 vs. 3/1000, Peto OR: 1,18 (95% KI 0,40; 3,51); I² = 59%, 10 RCTs, n = 4035, **very low-certainty evidence**.			

Zitat	Charakteristika desSR	Ergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar

2.1.4 Kombinationstherapie aus ICS/Salmeterol

Zitat	Charakteristika desSR	Ergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
Cates CJ. Inhaled steroids with and without regular salmeterol for asthma: Serious adverse events. Cochrane Database Syst Rev 2018; 12(12):CD006922. https://www.ncbi.nlm.nih.gov/pubmed/30521673	**Fragestellung:** To assess risks of mortality and non-fatal serious adverse events (SAEs) in trials that randomised participants with chronic asthma to regular salmeterol and ICS versus the same dose of ICS. **Suchzeitraum**: 10/2018 **Population**: adults and children with asthma of any severity **Intervention:** regular salmeterol and ICS (in separate or combined inhalers) **Control:** same dose of ICS of at least 12 weeks in duration **primäre Endpunkte:** • All-cause mortality • All-cause non-fatal SAEs **Body of Evidence:** - 41 studies (27,951 participants) in adults and adolescents, along with eight studies (8453 participants) in children - checked FDA submissions in relation to salmeterol	`- All except 542 adults (and none of the children) were given salmeterol and fluticasone in the same (combination) inhaler. **primary outcomes** All-cause mortality - 11/14,233 adults taking regular salmeterol and ICS died, as did 13 of 13,718 taking regular ICS at the same dose - 1/1000 vs. 1/1000; Peto OR: 0,80 (95% KI 0,36; 1,78); I² = 0% ,41 RCTs, n = 27,951; **moderate-certainty evidence** - No children died, and no adults or children died of asthma, so we remain uncertain about mortality in children and about asthma mortality in any age group Non-fatal serious adverse events *Erwachsene* - A total of 332 adults receiving regular salmeterol with ICS experienced a non-fatal SAE of any cause, compared to 282 adults receiving regular ICS - 23/1000 vs. 21/1000; peto OR: 1,14 (95% KI 0,97; 1,33); I² = 0%, 41 RCTs, n = 27,951; **moderate-certainty evidence** *Kinder* Sixty-five of 4229 children given regular salmeterol with ICS suffered an SAE of any cause, compared to 62 of 4224 children given regular ICS - 15/1000 vs. 15/1000; Peto OR: 1.04 (95% KI 0,73; 1,48); I² = 0%, 8 RCTs, n = 8453; **moderate-certainty evidence** **secondary outcome (relevante)** asthma-related SAEs *Erwachsene* - Eighty and 67 adults in each group, respectively, experienced an asthma-related non-fatal SAE. - 6/1000 vs. 5/1000; Peto OR: 1,15 (95% KI 0,83; 1,59); I² = 0%, 41 RCTs, n = 27,951; **low-certainty evidence**	AMSTAR2: Qualität des Reviews: - **high** AMSTAR-Score kritische Kriterien: 7/7	siehe endpunktspezifische GRADE-Bewertung des Reviews	keine Bedarfstherapie; Update von Ref. 90 in NVL 4. Auflage: Cates CJ, Schmidt S, Ferrer M, Sayer B, Waterson S. Regular treatment with salmeterol and inhaled steroids for chronic asthma: serious adverse events. Cochrane Database of Systematic Reviews 2013, Issue 3. [DOI: 10.1002/14651858.CD006922.pub3]

Zitat	Charakteristika desSR	Ergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
		Kinder - 29 children taking salmeterol and ICS and 23 children taking ICS alone reported asthma-related events - 7/1000 vs. 5/1000; Peto OR: 1,25 (95% KI 0,72; 2,16); I² = 0%, 8 RCTs, n = 8453; **moderate-certainty evidence**			

2.1.5 Kombinationstherapien aus Formoterol/ICS und Salmeterol/ICS

Zitat	Charakteristika desSR	Ergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
O'Shea O. Regular treatment with formoterol and an inhaled corticosteroid versus regular treatment with salmeterol and an inhaled corticosteroid for chronic asthma: Serious adverse events. Cochrane Database Syst Rev 2021; 4(4):CD007694. https://www.ncbi.nlm.nih.gov/pubmed/33852162	**Fragestellung:** To assess risks of mortality and non-fatal serious adverse events in trials that have randomised patients with chronic asthma to regular formoterol and an inhaled corticosteroid versus regular salmeterol and an inhaled corticosteroid. **Suchzeitraum:** 02/2021 **Population:**patients of any age and severity of asthma **Intervention:** regular formoterol vs. **Control:** regular salmeterol (each with a randomised inhaled corticosteroid) **Primary outcomes:** • All-cause mortality • All-cause non-fatal serious adverse events **Body of Evidence:** 21 Studien (n=11,572 Erwachsene + Jugendliche); 2 Studien (n= 723 Kinder) Erwachsene und Jugendliche: n=7 studies compared formoterol and budesonide to salmeterol and fluticasone (N = 7764), n=6 compared formoterol and beclomethasone to salmeterol and fluticasone (N = 1923), n=2 compared formoterol and mometasone to salmeterol and fluticasone (N = 1126), n=2 compared formoterol and fluticasone to salmeterol and	**all-cause Mortality** The certainty of evidence for allcause mortality was low, as there were not enough deaths to permit any precise conclusions regarding the risk of mortality on combination formoterol versus combination salmeterol. **all-cause SAEs** *Erwachsene* - In all, 201 adults reported non-fatal SAEs. - In studies comparing formoterol and budesonide to salmeterol and fluticasone: 77 in the formoterol arm and 68 in the salmeterol arm (Peto OR 1.14, 95% CI 0.82 to 1.59; 5935 participants, 7 studies; **moderate-certainty evidence**). - In the formoterol and beclomethasone studies, there were 12 adults in the formoterol arm and 13 in the salmeterol arm with events (Peto OR 0.94, 95% CI 0.43 to 2.08; 1941 participants, 6 studies; **moderate-certainty evidence**). - formoterol and mometasone studies: 18 in the formoterol arm and 11 in the salmeterol arm (Peto OR 1.02, 95% CI 0.47 to 2.20; 1126 participants, 2 studies; moderate-certainty evidence). One adult in the formoterol and fluticasone studies in the salmeterol arm experienced an event (Peto OR 0.05, 95% CI 0.00 to 3.10; 293 participants, 2 studies; **low-certainty evidence)**. - Another adult in the formoterol and budesonide compared to salmeterol and budesonide study in the formoterol arm had an event (Peto OR 7.45, 95% CI 0.15	AMSTAR2: Qualität des Reviews: - **low** AMSTAR-Score kritische Kriterien: - 6/7 - used no appropriate methods for statistical combination of results - Review aufgeführt, da Update der Vorgängerversion (4. Aufl.)	siehe endpunktspezifische GRADE-Bewertung des Reviews	keine Bedarfstherapie Update von Ref. 89 in NVL 4. Auflage: Cates CJ, Jaeschke R, Schmidt S, et al. Regular treatment with formoterol and inhaled steroids for chronic asthma: Serious adverse events. Cochrane Database Syst Rev 2013; 6:CD006924. DOI: 10.1002/14651858.CD006924.pub3. http://www.ncbi.nlm.nih.gov/pubmed/23744625.

Zitat	Charakteristika desSR	Ergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
	fluticasone (N = 790), and n=1 compared formoterol and budesonide to salmeterol and budesonide (N = 229). - were of at least 12 weeks' duration	to 375.68; 229 participants, 1 study; **low-certainty evidence**). **asthma-related SAEs** *Erwachsene* Only 46 adults were reported to have experienced asthma-related serious adverse events. The certainty of the evidence was low to very low due to the small number of events and the absence of independent assessment of causation. *Kinder* The two studies in children compared formoterol and fluticasone to salmeterol and fluticasone. No deaths and no asthma-related serious adverse events were reported in these studies. Four all-cause serious adverse events were reported: three in the formoterol arm, and one in the salmeterol arm (Peto OR 2.72, 95% CI 0.38 to 19.46; 548 participants, 2 studies; **low-certainty evidence**).			

2.1.6 Anti-Interleukin 13 / Anti-Interleukin 4-Antikörper

Zitat	Charakteristika desSR	Ergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
Gallagher A. Anti-interleukin-13 and anti-interleukin-4 agents versus placebo, anti-interleukin-5 or anti-immunoglobulin-E agents, for people with asthma. Cochrane Database Syst Rev 2021; 10(10):CD012929. https://www.ncbi.nlm.nih.gov/pubmed/34664263	**Fragestellung:** To assess the efficacy and safety of anti-interleukin-13 or anti-interleukin 4 agents, compared with placebo, anti immunoglobulin E agents, or anti-interleukin-5 agents, for the treatment of children, adolescents, or adults with asthma. **Suchzeitraum:** 10/2020 **Population**: adolescents and adults (aged 16 years or older) or children (younger than 16 years) with asthma) **Intervention**: anti-interleukin-13 or -4 agents **Control**: Placebo **Body of Evidence:** 29 RCTs, randomly assigning 10,604 people to receive an anti-interleukin-13 (intervention) or anti-interleukin-4 agent (intervention), or placebo (comparator) - 4 studies (2835 participants) evaluated dupilumab (300 mg once every week (Q1W), 200 mg once every 2 weeks (Q2W), 300 mg Q2W, 200 mg once every 4 weeks (Q4W), 300 mg Q4W, each administered by subcutaneous injection)	Keine Daten für Kinder > 12 Jahren Q1W = once every weeks Q2W = once every two weeks Q4W = once every 4 weeks **Serious adverse events** Dupilumab 300 mg SC (Q1W) - Odds Ratio (M-H, Fixed, 95% CI) 0.32 [0.03, 3.18], 1 RCT, n = 104 Dupilumab 200 mg SC Q2W - Odds Ratio (M-H, Fixed, 95% CI) 0.96 [0.60, 1.54]; I² = 0%, 2 RCTs, n = 1131 Dupilumab 200 mg SC Q4W - Odds Ratio (M-H, Fixed, 95% CI) 0.77 [0.15, 3.98], 1 RCT, n = 189 Dupilumab 300 mg SC Q2W - Odds Ratio (M-H, Fixed, 95% CI) 1.16 [0.76, 1.77]; I² = 0%, 3 RCTs, n = 1359 Dupilumab 300 mg SC Q4W - Odds Ratio (M-H, Fixed, 95% CI) 1.40 [0.39, 5.06], 1 RCT, n = 197 **Change from baseline in ACQ score** Dupilumab 300 mg SC Q1W - Mean Difference (IV, Fixed, 95% CI) -0.73 [-1.15, -0.31], 1 RCT, n = 104 Dupilumab 200 mg SC Q2W - Mean Difference (IV, Fixed, 95% CI) -0.38 [-0.51, -0.25]; I² = 0%, 2 RCTs, n = 1114 Dupilumab 300 mg SC Q2W - Mean Difference (IV, Fixed, 95% CI) -0.27 [-0.39, -0.15]; I² = 16%, 3RCTs, n = 1341 Dupilumab 200 mg SC Q4W - Mean Difference (IV, Fixed, 95% CI) -0.18 [-0.53, 0.17]; 1	AMSTAR2: Qualität des Reviews: **- low** AMSTAR-Score kritische Kriterien: - 6/7 - did not explore possible small study and publication biases	siehe endpunktspezifische GRADE-Bewertung des Reviews	Voyage-Studie für Kinder ab 6 Jahren identifiziert (waiting assessment) eingeschlossene Studien für Dupilumab: Castro 2018 + Rabe 2018 (Phase III) in systematischer Recherche zur Vorversion identifiziert Wenzel 2013 und 2016: ebenfalls identifiziert, jedoch aufgrund iterativen Vorgehens (da Phase 2b) zurückgestellt

Zitat	Charakteristika desSR	Ergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
		RCT, n = 158 Dupilumab 300 mg SC Q4W Mean Difference (IV, Fixed, 95% CI) -0.20 [-0.54, 0.14]; 1 RCT, n = 163 **Exacerbation requiring hospitalisation/ED/OCS (rate ratio)** Dupilumab 200mg SC Q2W - Rate Ratio (IV, Fixed, 95% CI) 0.51 [0.40, 0.64]; I² = 10%, 2 RCTs, n = 1135 Dupilumab 200 mg SC Q4W - Rate Ratio (IV, Fixed, 95% CI) 0.46 [0.18, 1.16]; 1 RCT, n =195 Dupilumab 300mg SC Q2W - Rate Ratio (IV, Fixed, 95% CI) 0.52 [0.42, 0.65]; I² = 28%, 2 RCTs, n = 1144 Dupilumab 300 mg SC Q4W - Rate Ratio (IV, Fixed, 95% CI) 0.67 [0.29, 1.55]; 1 RCT, n =197			

2.1.7 Anti-IL-5-Antikörper

Zitat	Charakteristika desSR	Ergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
Farne HA. Anti-IL-5 therapies for asthma. Cochrane Database Syst Rev 2022; 7(7):CD010834. https://www.ncbi.nlm.nih.gov/	**Fragestellung:** To compare the effects of therapies targeting IL-5 signalling (anti-IL-5 or anti-IL-5RP) with placebo on exacerbations, health-related quality of life (HRQoL) measures and lung function in adults and children with chronic asthma, and specifically in those with eosinophilic asthma refractory to existing treatments **Population:** adults and children with asthma **Intervention:** mepolizumab (s.c. + i.v.), reslizumab (s.c. + i.v.) or benralizumab (s.c.)	The anti-IL-5 treatments assessed reduced rates of 'clinically significant' asthma exacerbation by approximately half in participants with severe eosinophilic asthma on standard care (at least medium-dose ICS with poorly controlled disease (either two or more exacerbations in the preceding year or ACQ score of 1.5 or more), except for reslizumab SC. **clinically significant exacerbation (rate ratios)** - mepolizumab s.c.: 0.45 (95% CI 0.36 to 0.55); I² = 0%, 2 RCTs, n = 936 **high-certainty evidence** - mepolizumab i.v.: 0.53 (95% CI 0.44 to 0.64); I² = 0%, 3 RCTs, n = 751, **moderate-certainty evidence**	AMSTAR2: Qualität des Reviews: - **high** AMSTAR-Score kritische Kriterien: 7/7	siehe endpunktspezifische GRADE-Bewertung des Reviews	Update des Reviews von 2017 (dieser bereits) in 4.Auflage NVL Asthma inkludiert)

Zitat	Charakteristika desSR	Ergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
pubmed/35838542	**Control:** placebo Body of Evidence: - 6 RCTs: mepolizumab, - 5 RCTS: reslizumab, - 6 RTCs:benralizumab **Definition:** 'clinically significant' asthma exacerbation: treatment with systemic corticosteroids for three days or more	- reslizumab i.v.: 0.43 (95% CI 0.33 to 0.55); I² = 0%, 2 RCTs, n = 953, **high-certainty evidence** - reslizumab s.c.: 0.79 (0.56 to 1.11); 1 RCT, n = 464, **high-certainty evidence** - benralizumab s.c.: 0.59 (95% CI 0.52 to 0.66); I² = 21%, 4 RCTs, n = 3112 **high-certainty evidence** Non-eosinophilic participants treated with benralizumab also showed a significant reduction in exacerbation rates, an effect not seen with reslizumab i.v., albeit in only one study. No data were available for non-eosinophilic participants treated with mepolizumab. **Mepolizumab: Children 6-17 years** - one study on children and adolescents, which has not yet been published in full, are consistent with those on adults - minimum cut-off of 150 cells or more per µl for inclusion in the study - baseline-treatment: For those aged 6-11 years, treatment with at least medium- to high-dose ICS. For those ≥ 12 years of age, treatment with at least medium to high-dose ICS in combination with LABA - Intervention: Mepolizumab 40 mg (s.c.) for 6-11 year-olds, 100 mg (s.c.) for 12-17 year-olds every 4 weeks - reduction in clinically significant exacerbations in the intervention group (rate ratio 0.73, 95% CI 0.56 to 0.95)			

2.1.8 Spezifische (Allergen-)Immuntherapie

Jahr	Zitat	Charakteristika des SR	Ergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
2020	Fortescue R. Sublingual immunotherapy for asthma. Cochrane Database Syst Rev 2020; 9(9):CD0112	Allgemeine Angaben zur Studie: (keine) Metaanalyse, nur RCT/auch Kohortenstudien; HTA etc. **Fragestellung:**To assess the elicacy and safety of sublingual immunotherapy compared with placebo or standard care for adults and children with asthma.	Baseline-Charakteristika - at least 80% of trial participants had a diagnosis of asthma **Primary outcomes** <u>exacerbation requiring ED or hospital visit:</u> - SLIT may reduce exacerbations compared with placebo or usual care, but the evidence is very uncertain (104/1000 vs. 250/1000; OR 0,35 (95% KI 0,10; 1,20); I² = 0%, 2 studies, n = 108; **GRADE: very low**) <u>QoL</u> - 9 studies reporting quality of life could not be combined in a metaanalysis	AMSTAR2: Qualität des Reviews: - **high** AMSTAR-Score kritische Kriterien: 7/7	siehe endpunktspezifische GRADE-Bewertung des Reviews	Update des Reviews von 2015 (dieser war bereits in 4.Auflage NVL Asthma inkludiert)

Jahr	Zitat	Charakteristika des SR	Ergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
	93. https://www.ncbi.nlm.nih.gov/pubmed/32926419.	**Suchzeitraum**: 29 October 2019 **Population:** adults and children with asthma of any severity and with any allergen-sensitisation pattern. **Intervention:** sublingual immunotherapy **Control:** placebo **or:** SLIT as an add-on to standard asthma management **Outcome:** - asthma exacerbations requiring a visit to the emergency department (ED) or admission to hospital - validated measures of quality of life - all-cause serious adverse events (SAEs). **Body of Evidence:** 66 studies (23 studies recruited adults and teenagers; 31 recruited only children; 3 recruited both; and 9 did not specify)	and, whilst the direction of effect mostly favoured SLIT, the effects were often uncertain and small. SAEs - SLIT likely does not increase SAEs compared with placebo or usual care, and analysis by risk difference suggests no more than 1 in 100 people taking SLIT will have a serious adverse event (16/1000 vs. 20/1000; RD −0.0004 (95% KI −0,0072; 0,0064); I^2 = 0%, 29 studies, n = 4810; **GRADE: moderate**) **Secondary outcomes:** - asthma symptom and medication scores were mostly measured with non-validated scales, which precluded meaningful meta-analysis or interpretation, but there was a general trend of SLIT benefit over placebo. - Changes in ICS use (MD −17.13 Og/d (95% KI −61,19; 26,93); I^2 = 0%, 3 RCTs, n = 778, **GRADE: low**), exacerbations requiring oral steroids (studies = 2; no events), and bronchial provocation (SMD 0.99 (95% KI 0,17; 1,82); I^2 = 85%, 5 RCTs, n = 200; **GRADE: low**) were not often reported. Results were imprecise and included the possibility of important benefit or little effect and, in some cases, potential harm from SLIT. **Sicherheit** More people taking SLIT had adverse events of any kind compared with control (634/1000 vs. 465/1000; OR 1,99 (95% KI 1,49; 2.67); I^2 = 44% , 27 RCTs, n = 4251, **GRADE: high**), but events were usually reported to be transient and mild.			

2.2 Fixkombination als Bedarfstherapie in Stufe 1 und 2

2.2.1 Evidenzbericht

Aufgrund möglicher neuer Daten zum Thema wurde eine Recherche-Update sowohl für Erwachsene, als auch für Kinder und Jugendliche durchgeführt. Die Grundlage für die systematischen Recherchen zu den Fixkombinationen als Bedarfstherapie in Stufe 1 und 2 bildete der vorab identifizierte Cochrane Review (Crossingham 05/2021: Combination fixed-dose beta agonist and steroid inhaler as required for adults or children with mild asthma, www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013518.pub2/full) [3] (Kapitel 2.1.1 Fixkombination als Bedarfstherapie in Stufe 1 und 2).

Die im Cochrane Review [3] gepoolten Studien (SYGMA 1 [4], SYGMA 2 [5], PRACTICAL [6], Novel START [7]) wurden bereits in der 4. Auflage der NVL Asthma aufgeführt und diskutiert [8,9]. Im Recherche-Update für die bedarfsorientierte Anwendung einer Fixkombination Formoterol/ICS konnten keine zur Fragestellung passenden neuen RCTs identifiziert werden.

Auch für die bedarfsorientierte Anwendung einer Fixkombination aus SABA/ICS konnten in einer weiteren systematischen Recherche keine neuen RCT identifiziert werden. Der im Cochrane Review identifizierte, jedoch nicht eingeschlossene RCT von Papi et al. (2007) [10], wurde gesondert extrahiert und bewertet.

2.2.2 SABA/ICS

Zitat	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
Papi a. Rescue Use of Beclomethasone and Albuterol in a Single Inhaler for Mild Asthma. N Engl J Med 2007;356:2040-52. https://pubmed.ncbi.nlm.nih.gov/17507703/	**Studiendesign:** 6 month, double-blind, double-dummy, randomized, parallel-group trial. **Population:** patients with mild asthma (age: 18-65); n=455 **4-week run-in period:** 250 µg inhaled beclomethasone dipropionate twice daily and albuterol on an as-needed basis. **Intervention:** · placebo (2x/d) + 250 µg beclomethasone and 100 µg albuterol in a single inhaler as needed (as-needed combination therapy) **Vergleiche:** · placebo (2x/d) + 100 µg albuterol as needed (as-needed albuterol therapy) · 250 µg of beclomethasone (2x/d) and 100 µg of albuterol as needed (regular beclomethasone therapy); or · 250 µg beclomethasone and 100 µg albuterol in a single inhaler (2x/d) + 100 µg albuterol as needed (regular combination therapy) **Primary outcome:** morning peak expiratory flow rate **Secondary outcomes** (i) the mean value of evening PEF measured during the last 2 weeks of treatment, (ii) daily variability of PEF measured during the last 2 weeks of treatment; (iii) the percentage of days without the use of albuterol and/or without asthma symptoms during the last 2 weeks of treatment; (iv) the asthma symptom score during the last 2	**Baseline-Patientencharakteristika:** weitestgehend ausgeglichen zwischen allen 4 Gruppen **Effektivität sekundärer Endpunkte:** · Daytime asthma symptom score · Nighttime asthma symptom score · Nocturnal awakening (no.) · Symptom-free days (%) · Rescue medication (puffs/day) >> siehe Tabelle 2 Publikation · asthma exazerbations >> siehe Tabelle C im Supplement **authors conclusion**: In patients with mild asthma, the symptom driven use of inhaled beclomethasone (250 µg) and albuterol (100 µg) in a single inhaler is as effective as regular use of inhaled beclomethasone (250 µg twice daily) and is associated with a lower 6-month cumulative dose of the inhaled corticosteroid.	**Selection bias** Randomisierung: **low** Allocation concealment: **low** **Performance bias** Verblindung von Teilnehmern und Personal: **low** **Detection bias** Verblindung der Ergebnisevaluation: **unclear** **Attrition bias** Verlust von Studienteilnehmern/ fehlende Daten: **low** ITT-Analyse: modifizierte/volle ITT durchgeführt (Resultate gleich) **Reporting bias** selektive Ergebnisdarstellung: **low** **Andere Biasursachen** Baseline imbalance: **low** Interessenkonflikte/ Sponsoring: Chiesi Farmaceutici	1) Verzerrungsrisiko (RoB-Bewertung): niedrig 2) Präzision (Fallzahl, Eventzahl, KI-Weite): na 3) Direktheit/Übertragbarkeit auf Fragestellung: gut, wenn Beclomethason-Dosierung für Standardpartikelgröße gilt (= dann niedrigdosiert) 4) Konsistenz: na	Unterscheidung entsprechen ICS-Vergleichstabelle (NVL Asthma, 4. Auflage) zwischen Standardpartikelgröße vs. feiner Partikelgröße für das hier verabreichte Beclomethason anhand Registrierungsdaten (clinicaltrials.gov) oder vorliegender Publikation nicht möglich, daher in Evidenztabelle aufgeführt Im Supplement: Clenil Compositum 250 MDI, Chiesi = vermutlich Standardpartikelgröße?

Zitat	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
	weeks of treatment; (v) the number of exacerbations; (vi) the time to first exacerbation; (vii) changes from baseline lung function parameters and (viii) changes from baseline asthma clinical/symptoms scores. **Studienzeitraum:** recruited 08/2002 - 09/2004 **Statistik:** testet superiority or equivalence				

2.3 Dreifach-Fixkombination (LAMA/LABA/ICS)

2.3.1 Evidenzbericht

Aufgrund der Zulassungserweiterung für die Dreifach-Fixkombination (Trimbow: Beclometason/Formoterol/Glycopyrronium) für Patient*innen mit Asthma wurde eine systematische Recherche zum Thema für alle zur Verfügung stehenden Präparate durchgeführt. Es wurden die Datenbanken von Medline (via Pubmed) und der Cochrane Library (inklusive der Registerdaten) genutzt. Es konnten Phase III-RCTs mit den Wirkstoffkombinationen Beclomethason/Formoterol/Glycopyrronium (n=2), Mometason/Indacaterol/Glycopyrronium (n=2) und Fluticason/Vilanterol/Umeclidinium (n=1) identifiziert werden; alle als Fixkombinationen (single-inhaler).

Von den insgesamt 5 identifizierten RCT verglichen n= 2 eine Dreifach-Fixkombination mit einer open label ICS/LABA-Fixkombination + Tiotropium. Die Populationen der Studien (Pat. > 18 Jahre mit „unkontrolliertem Asthma“) sowie die untersuchten Interventionen entsprachen dabei der PICO-Fragestellung, sodass von einer guten Direktheit auszugehen ist.

2.3.2 Beclomethason/Formoterol/Glycopyrronium

Zitat	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
Virchow JC. Single inhaler extrafine triple therapy in uncontrolled asthma (TRIMARAN and TRIGGER): Two double-blind, parallel-		**Baseline-Charakteristika:** hinsichtlich Alter, Geschlecht, Gewicht; Krankheitsdauer; Rauchhistorie, Exazerbationen im letzten Jahr; Reversibilitätstestung, ACQ-7-Score zwischen den einzelnen Gruppen in den jeweiligen Studien weitestgehend ausgeglichen **Serious adverse events**	**Selection bias** Randomisierung: **low** Allocation concealment: **low** **Performance bias** Verblindung von Teilnehmern und	**Aussagesicherheit der Evidenz: moderat** 1) Verzerrungsrisiko: -1 (aufgrund des open label-Konzepts der Vergleichsintervention ist die Verblindung von Studien-	**Registereinträge:** TRIMARAN: https://www.clinicaltrialsregister.eu/ctr-search/trial/2015-000716-18/results TRIGGER:

Zitat	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
group, randomised, controlled phase 3 trials. Lancet 2019; 394(10210):1737–49. https://www.ncbi.nlm.nih.gov/pubmed/31582314.		Four patients had treatmentrelated serious adverse events, one in TRIMARAN in the BDP/FF/G group and three in TRIGGER—one in the BDP/FF/G and two in the BDP/FF group. Three patients in the BDP/FF/G group in TRIMARAN and two patients in TRIGGER —one in the BDP/FF/G group and one in the BDP/FF group—had adverse events leading to death. None of the deaths were considered as related to treatment. --> siehe Tabelle 2 (S. 10) in der Publikation **Primäre Endpunkte:** The coprimary endpoints for both studies were morning predose FEV1 at week 26 and the rate of moderate and severe exacerbations over 52 weeks in each study.	Personal: **low** (**high** für TRIGGER) **Detection bias** Verblindung der Ergebnisevaluation: **unclear** **Attrition bias** Verlust von Studienteilnehmern/ fehlende Daten: **low** ITT-Analyse: nein (all randomised patients receiving at least one dose of study drug) **Reporting bias** selektive Ergebnisdarstellung: **low** **Andere Biasursachen** Baseline imbalance: **low** Interessenkonflikte/ Sponsoring: Chiesi Farmaceutici *The funder of the study had a role in the study design and data analysis, oversaw study conduct, and was responsible for study report preparation.*	teilnehmenden und Personal mit „hoch“ eingeschätzt worden) 2) Präzision: +/-0 3) Direkt-heit/Übertragbarkeit: +/-0 (Vergleichsintervention aus LAMA/LABA/ICS ist mit Studienintervention gleichberechtigt und vergleichbar)	https://www.clinicaltrialsregister.eu/ctr-search/trial/2015-000717-40/results In der Publikation wurden Daten der beiden Studien gepoolt; in dieser Evidenzdarstellung jedoch jeweils entsprechend der Dosierungen in den Einzelstudien aufgeführt
	Studienname: TRIGGER **Studiendesign:** parallel-group, double-blind, randomised, active-controlled, phase 3 trial **Population:** **-** adults (aged 18–75 years) with uncontrolled asthma, a history of one or more exacerbations in the previous year, and previously treated with ICS (high dose) plus LABA - Randomisation: 2:2:1 **Intervention:** CHF 5993 - fixed combination: beclometasone/formoterol/glycopyrronium **200**/6/12.5 µg pMDI **Vergleich:** CHF 1535 - fixed combination: beclometasone/formoterol **200**/6 µg pMDI oder - open -label: fixed combination: beclometasone/formoterol 200/6 µg pMDI + Tiotropium 2.5 µg - patients were initially treated with 200 µg BDP and 6 µg FF for 2 weeks before randomisation - rescue medication: Salbutamol (not within 6 hours before any visit)	**Exacerbations** - reductions in the rate of moderate and severe exacerbations of 12% - rate ratio BDP/FF/GB 200/6/12.5 µg vs BDP/FF 200/6 µg RR 0.88 (95% CI 0.751; 1.03); n=1142 - BDP/FF/GB 200/6/12.5 µg vs. BDP/FF 200/6 µg + TIO 2.5µg: RR 1,07 (95%CI 0.88 - 1.3); n=858 Ausgewählte sekundäre Endpunkte: BDP/FF/GB 200/6/12.5 µg vs. BDP/FF 200/6 µg **Asthma Control Questionnaire© (ACQ)-7 response at Week 52** - OR 1.161 (0.912; 1.478); n=1074 **Time to first moderate or severe asthma exacerbation** - HR 0.799 (0.688; 0.929); n=1142			

Zitat	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
	Studiendauer: 04/2016 - 05/2018 **study locations:** international, 17 countries **Responsible Party:** Chiesi Farmaceutici S.p.A	**Change from baseline in the percentage of asthma control days in each inter-visit period, over the 52-week treatment period** - Adjusted MD: 3.513 (0.379; 6.646); n=1139 BDP/FF/G vs BDP/FF +TIO **Time to first moderate or severe asthma exacerbation** - HR 0·97 (0·81–1·18)			
	Studienname: TRIMARAN **Studiendesign:** parallel-group, double-blind, randomised, active-controlled, phase 3 trial **Population:** - adults (aged 18–75 years) with uncontrolled asthma, a history of one or more exacerbations in the previous year, and previously treated with ICS (medium dose) plus LABA - Randomisation: 1:1 **Intervention:** CHF 5993 - fixed combination: beclometasone/formoterol/glycopyrronum **100**/6/12.5 µg pMDI **Vergleich:** CHF 1535 - fixed combination: beclometasone/formoterol **100**/6 µg pMDI - patients were initially treated with 100 µg BDP and 6 µg FF for 2 weeks before randomisation - rescue medication: Salbutamol (not within 6 hours before any visit) **Studiendauer:** 02/2016 - 05/2018 **study locations:** international; 16 countries **Responsible Party**: Chiesi Farmaceutici S.p.A	**Exacerbations** - reductions in the rate of moderate and severe exacerbations of 15% - RR 0·85, 95% CI 0·73–0·99; n=1149 Ausgewählte sekundäre Endpunkte: BDP/FF/GB 100/6/12.5 µg vs. BDP/FF 100/6 µg **Asthma Control Questionnaire©-7 (ACQ-7) response at Week 52** - OR 1.072 (0.843; 1.362); n=1149 **Time to first moderate or severe asthma exacerbation** - HR 0.842 (0.727; 0.975); n=1149 **Change from baseline in the percentage of asthma control days in each inter-visit period, over the 52-week treatment period** - Adjusted MD 1.286 (-1.887; 4.459); n=1148			Kein direkter Vergleich: Dreifach-Fixkombination mit einer open label Dreifach-Kombi → für Einschätzung daher hinten angestellt

Nutzenbewertungen/Sicherheitsdaten

Die Nutzenbewertung des G-BA findet sich unter folgendem Link: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/653/

2.3.3 Mometason/Indacaterol/Glycopyrronium

Zitat	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
Gessner C. Fixed-dose combination of indacaterol/glycopyrronium/mometasone furoate once-daily versus salmeterol/fluticasone twice-daily plus tiotropium once-daily in patients with uncontrolled asthma: A randomised, Phase IIIb, non-inferiority study (ARGON). Respir Med 2020; 170:106021. https://www.ncbi.nlm.nih.gov/pubmed/32843164.	**Studienname:** ARGON **Studiendesign:** randomised, active-controlled Phase IIIb, non-inferiority, 24-week, parallel-group, open-label study **Population:** Asthma; uncontrolled - aged ≥18 years, with Asthma for ≥ 6 month prior screening - history of ≥1 severe asthma exacerbation (required medial care (physician, ER visit or hospitalisation) and systemic corticosteroid treatment for at least 3 d in the past 12 month - symptomatic (Asthma Control Questionnaire [ACQ]-7 ≥1.5) despite treatment with LABA/ICS medium- or high-dose - randomised 1:1:1 **Intervention:** Indacaterol/glycopyrronium/mometasone (via Breezhaler®) - high dose 150/50/160 µg; 1x/d - medium dose 150/50/80 µg; 1x/d **Vergleich:** Salmeterol/Fluticasone + Tiotropium (via Accuhaler® / Respimat®) 50/500 µg (2x/d) + 5 µg (1x/d) **Run-in period (2 weeks):** Open-label SAL/FLU 50/250 µg or 50/500 µg; 2x/d **Rescue medication:** 100 µg salbutamol MDI or equivalent albuterol MDI **Studiendauer:** 02/2018 - 07/2019 **Study locations:** international, 21 countries **Responsible Party:** Novartis Pharmaceuticals	**Baseline-Charakteristika:** Gruppen hinsichtlich Alter, Geschlecht, Rauchhistorie, Erkrankungsdauer, Anzahl der Asthmaexazerbationen im letzten Jahr, AQLQ, ACQ-7, prior asthma medication weitestgehend ausgeglichen **Change From Baseline in Asthma Quality of Life Questionnaire (AQLQ) Total Score after 24 weeks** · IND/GLY/MF medium-dose vs. SAL/FLU high-dose +TIO: - LS Mean (95%CI): -0.038 (-0.139; --); n=871) · IND/GLY/MF high-dose vs. SAL/FLU high-dose +TIO: - LS Mean (95%CI): 0.073 (-0.027; --); n= 888 **Adverse events** Total subjects affected by serious adverse events: subjects affected / exposed · IND/GLY/MF medium-dose: 14 / 474 (2.95%) · IND/GLY/MF high-dose: 18 / 476 (3.78% · SAL/FLU high-dose +TIO: 19 / 475 (4.00%) <u>Ausgewählte sekundäre Endpunkte</u> **Change from Baseline in Asthma Control Questionnaire (ACQ-7) Total Score** IND/GLY/MF medium-dose vs. SAL/FLU high-dose +TIO: week 24 - LS Mean (95%CI): -0.032 (-0.125; 0.06), n=894) IND/GLY/MF high-dose vs. SAL/FLU high-dose +TIO: week 24 - LS Mean (95%CI): -0.124 (-0.216; -0.032); n=901 **Change from Baseline in AQLQ Total Score** IND/GLY/MF medium-dose vs. SAL/FLU high-dose +TIO: week 16	**Selection bias** Randomisierung: **low** Allocation concealment: **low** **Performance bias** Verblindung von Teilnehmern und Personal: **high** **Detection bias** Verblindung der Ergebnisevaluation: **low** **Attrition bias** Verlust von Studienteilnehmern/ fehlende Daten: **low** ITT-Analyse: nein (all randomised patients receiving at least one dose of study drug) **Reporting bias** selektive Ergebnisdarstellung: **unclear** **Andere Biasursachen** Baseline imbalance: **low** Interessenkonflikte/ Sponsoring: Responsible Party: Novartis Pharmaceuticals weiteres: Follow-Up= 7d	**Aussagesicherheit der Evidenz: niedrig** 1) Verzerrungsrisiko: -1 (aufgrund des open label-Konzepts der Vergleichsintervention ist die Verblindung von Studienteilnehmenden und Personal mit „hoch“ eingeschätzt worden) 2) Präzision: +/-0 3) Direktheit/Übertragbarkeit: -1 (Studienintervention (neuere Wirkstoffe) unfair überlegen der Vergleichsintervention)	·non-inferiority study · kurzes Follow-Up-Periode (7 Tage) · keine Angaben bezüglich potentieller Adhärenzverbessserung · es wurden alle in den Registern erwähnten primären und sekundären EP abgebildet; jedoch in der Publikation zusätzlich noch Angaben zu Exazerbationen eingefügt: nicht a priori festgelegtes Outcome **Registereinträge:** https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2017-000136-34-ES https://clinicaltrials.gov/show/NCT03158311

Zitat	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
		- LS Mean (95%CI): 0.018 (-0.079; 0.115); n=864 IND/GLY/MF high-dose vs. SAL/FLU high-dose +TIO: week 16 - LS Mean (95%CI): 0.082 (-0.015; 0.179); n=871 **Annualised rate of exacerbations during Weeks 1–24** <u>moderate or severe asthma exacerbation</u> IND/GLY/MF medium-dose vs. SAL/FLU +TIO: - Rate Ratio (RR) 1,04 (95%CI 0,77; 1,39) IND/GLY/MF high-dose vs. SAL/FLU +TIO: -RR 0,88 (95%CI 0,65; 1,19) <u>severe asthma exacerbation</u> IND/GLY/MF medium-dose vs. SAL/FLU +TIO: - RR 1,22 (05%CI 0,85; 1,75) IND/GLY/MF high-dose vs. SAL/FLU +TIO: - RR 1,14 (95%CI 0,79; 1,31)			
Kerstjens HA. Once-daily, single-inhaler mometasone-indacaterol-glycopyrronium versus mometasone-indacaterol or twice-daily fluticasone-salmeterol in patients with inadequately controlled asthma (IRIDIUM): A randomised, double-blind, controlled phase 3 study. Lancet Respir	**Studienname:** IRIDIUM **Studiendesign:** randomised,double-blind, parallel-group, controlled phase 3 study; 52-week **Population:** uncontrolled asthma; n=3092 - aged 18 to 75 years with symptomatic asthma (ACQ-7 score of at least 1,5) despite treatment with medium-dose or high-dose ICS–LABA, at least one exacerbation in the previous year, and a percentage of predicted FEV1 of less than 80% - with a diagnosis of asthma for a period of at least 1 year before screening - receiving medium-dose or high-dose ICS–LABA for at least 3 months and at a stable dose for at least 1 month before	**Baseline-Charakteristika** hinsichtlich Alter, Geschlecht, Raucherstatus, Exazerbationen im letzten Jahr, Baseline ACQ-7, previous asthma treatment weitestgehend ausgeglichen **primärer Endpunkt**: change from baseline in trough FEV1 after 26 weeks **Adverse events** Overall, the incidence of adverse events was balanced across the treatment groups. Seven deaths were reported (one with medium-dose MF–IND–GLY, two with high-dose MF–IND–GLY, and four with high-dose MF–IND) during the study; none of these deaths was considered by the investigators to be caused by study drugs or other studyrelated factors.	**Selection bias** Randomisierung: **low** Allocation concealment: **low** **Performance bias** Verblindung von Teilnehmern und Personal: **low** **Detection bias** Verblindung der Ergebnisevaluation: **unclear** **Attrition bias** Verlust von Studienteilnehmern/ fehlende Daten: **unclear**		**Registereintrag:** https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2015-002899-25-LV *- full analysis set, which included all patients who were assigned a randomisation number and received at least one dose of study medication:* nur für prim. EP + sek. EP ACQ-7; alle anderen deskriptiv (*No multiplicity adjustments were applied for other secondary end-*

Zitat	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
Med 2020; 8(10):1000–12. https://www.ncbi.nlm.nih.gov/pubmed/32653074.	screening - no asthma exacerbation requiring systemic corticosteroids, hospitalisation, or emergency room visit within 6 weeks of screening - randomisation: 1:1:1:1:1 **Intervention:** medium-dose or high-dose Mometason /Indacaterol/Glycopyrronium single-inhaler - 80 /150 /50 µg; 1x/d (MF/IND/GLY medium-dose) - 160 /150 /50 µg; 1x/d (MF/IND/GLY high-dose) **Vergleich:** Mometason/Indacaterol single-inhaler - 160 /150 µg; 1x/d (MF/IND medium-dose) - 320 /150 µg; 1x/d (MF/IND high-dose) oder - Fluticasone/ Salmeterol 500/50 µg; 2x/d (FLU/SAL high-dose) - rescue medication: salbutamol or albuterol **Studiendauer:** 12/2015 - 06/2019 **study locations**: international, 41 countries **Responsible Party:** Novartis Pharma AG	<u>Ausgewählte sekundäre Endpunkte</u> **Annualised rate of exacerbations at week 52 in the full analysis set** Auswahl: All (mild, moderate, severe) asthma exacerbation; Unit: exacerbation per year: Mean (95%CI) MF/IND/GLY high-dose vs MF/IND high-dose - 0.74 (0.64 to 0.85) vs. 0.93 (0.82 to 1.06) - rate ratio 0.79 (0.66; 0.96); n=1226 MF/IND/GLY high-dose vs FLU/SAL high-dose - 0.74 (0.64 to 0.85) vs. 1.23 (1.08 to 1.39) - rate ratio 0.6 (0.5; 0.72); n=1227 MF/IND/GLY medium-dose vs MF/IND medium-dose - 0.86 (0.75 to 0.98) vs. 0.98 (0.86 to 1.11) - rate ratio 0.87 (0.72; 1.06); n=1223 MF/IND/GLY medium-dose vs FLU/SAL high-dose - 0.86 (0.75 to 0.98) vs. 1.23 (1.08 to 1.39) - rate ratio 0.7 (0.58; 0.84); n=1228 *--> Auswertungen nach Schwere der Exazerbation: siehe Abbildung 5 der Publikation* **Time to first hospitalization for asthma exacerbation (52 weeks)** MF/IND/GLY high-dose vs MF/IND high-dose - HR 0.66 (0.27; 1.63); n=1226 - 367.0 (2 to 416) vs. 367.0 (1 to 411) days	ITT-Analyse: nein **Reporting bias** selektive Ergebnisdarstellung: **low** **Andere Biasursachen** Baseline imbalance: **low** Interessenkonflikte/ Sponsoring: Novartis Pharma AG: had a role in the study design, data collection, and data analysis, oversaw study conduct, and was responsible for study report preparation. Medical writing support was funded by the study sponsor		*points and p values described for these are descriptive.)* Kein direkter Vergleich: Dreifach-Fixkombination mit einer open label Dreifach-Kombi → für Einschätzung daher hinten angestellt

Zitat	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
		MF/IND/GLY high-dose vs FLU/SAL high-dose - HR 1 (0.37; 2.66); n= 1227 - 367.0 (2 to 416) vs. 367.0 (1 to 416) days MF/IND/GLY medium-dose vs MF/IND medium-dose - HR 1.89 (0.8; 4.47); n=1223 - 367.0 (2 to 396) vs. 367.0 (1 to 408) days QMF/IND/GLY medium-dose vs FLU/SAL high-dose - HR 1.88 (0.8; 4.43) - 367.0 (2 to 396) vs. 367.0 (1 to 416) days **--> Auswertungen anderer sekundärer End-punkte (Auswahl) siehe auch Registerdaten o. Appendix:** - Asthma Control Questionnaire (ACQ-7) at Week 26 and Week 52 - Change from baseline in percentage of asthma symptom-free days over 52 weeks - Change from baseline in percentage of days with no daytime symptoms - Change from baseline in percentage of nights with no night-time awakenings over 52 weeks - Change from baseline in percentage of days with-out rescue medication use over 26 and 52 weeks - Asthma Quality of Life Questionnaire (AQLQ) at Week 52			

Nutzenbewertungen/Sicherheitsdaten

Die Nutzenbewertung des G-BA findet sich unter folgendem Link: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/577/

2.3.4 Fluticason/Vilanterol/Umeclidinium

Zitat	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Kommentar
Lee LA. Efficacy and safety of once-daily single-inhaler triple therapy (FF/UMEC/VI) versus FF/VI in patients with inadequately controlled asthma (CAPTAIN): A double-blind, randomised, phase 3A trial. Lancet Respir Med 2021; 9(1):69–84. https://www.ncbi.nlm.nih.gov/pubmed/32918892.	**Studienname:** CAPTAIN **Studiendesign:** double-blind, randomised, parallel-group, phase 3A, 24-52 weeks study **Population:** Subjects With Inadequately Controlled Asthma; n=2436 - ≥18 years, with inadequately controlled asthma (ACQ-6 score of ≥1·5) despite ICS/LABA for at least 12 weeks before pre-screening, with no changes to therapy in the 6 weeks before pre-screening - a documented health-care contact or a documented temporary change in asthma therapy for treatment of acute asthma symptoms in the year before screening, pre-bronchodilator FEV(1) between 30% and less than 85% of predicted normal value, and reversibility (defined as an increase in FEV(1) of ≥12% and ≥200 mL in the 20-60 min after four inhalations of albuterol or salbutamol) at screening. - randomisation: 1:1:1:1:1:1 **Intervention:** Fluticason/Vilanterol/Umeclidinium (single inhaler) - FF/UMEC/VI (100/31.25/25) µg; 1x/d - FF/UMEC/VI (100/62.5/25) µg; 1x/d - FF/UMEC/VI (200/31.25/25) µg; 1x/d - FF/UMEC/VI (200/62.5/25) µg; 1x/d **Vergleich:** - FF/VI (100/25) µg; 1x/d - FF/VI (200/25) µg; 1x/d - run-in period: open-label FP/SAL 250/50µg 3 weeks + - stabilisation period: open-label FF/VI 100/25 µg for all patients **Studiendauer:** 10/2016 - 02/2019 (in der Publikation: 12/2016 - 08/2018) **study locations:** international, 15 countries **Responsible Party:** GlaxoSmithKline	**Baseline-Charakteristika:** hinsichtlich Alter, Geschlecht, Gewicht, pre-study ICS-Dosis, Anzahl und Schwere der Exazerbationen in den letzten 12 Monaten, Bluteosinophile und FeNO beim Screening, Raucher-Historie weitestgehend ausgeglichen **primärer Endpunkt**: Mean Change From Baseline in Trough FEV1 at Week 24 **adverse events** - was similar across treatment groups (patients with at least one event ranged from 210 [52%] to 258 [63%]), with most commonly reported adverse events being nasopharyngitis (51 [13%]-63 [15%]), headache (19 [5%]-36 [9%]), upper respiratory tract infection (13 [3%]-24 [6%]). **SAEs** The incidence was similar across all groups (range 18 [4%]-25 [6%]). Three deaths occurred, of which one was considered to be related to study drug (pulmonary embolism in a patient in the FF/UMEC/VI 100/31·25/25 µg group). **Ausgewählte sekundäre Endpunkte:** **Annualized Rate of Moderate and Severe Asthma Exacerbations** <u>gepoolte Interventionsgruppen + gepoolte Vergleichsgruppen:</u> · FF/UMEC/VI (UMEC 31.25 µg) vs. FF/VI: - rate ratio 0.97 (0.81; 1.17); n=1622 · FF/UMEC/VI (UMEC 62.5 µg) vs. FF/VI: - rate ratio 0.87 (0.72; 1.05); n=1627 *By contrast with adding UMEC, the effects of higher dose FF on clinic trough FEV(1) and annualised moderate and/or severe exacerbation rate were increased in patients with higher baseline blood eosinophil count and exhaled nitric oxide.* <u>ungepoolte Interventions- und Vergleichsgruppen</u> · FF/UMEC/VI (100/31.25/25) µg vs FF/VI (100/25) µg - rate ratio 0,88 (0,68; 1,13) · FF/UMEC/VI (100/62.5/25) µg vs. FF/VI (100/25) µg -rate ratio 0,78 (0,61; 1,01)	**Selection bias** Randomisierung: **low** Allocation concealment: **low** **Performance bias** Verblindung von Teilnehmern und Personal: **low** **Detection bias** Verblindung der Ergebnisevaluation: **unclear** **Attrition bias** Verlust von Studienteilnehmern/ fehlende Daten: **low** ITT-Analyse: ja **Reporting bias** selektive Ergebnisdarstellung: **low** **Andere Biasursachen** Baseline imbalance: **low** Interessenkonflikte/ Sponsoring: The funder of the study had a role in study design, data collection, data analysis, data interpretation, and writing of the report	*"analysis of non-spirometry endpoints: FF/UMEC/VI for each UMEC dose were pooled and compared with pooled FF/VI data to increase the power and precision of the analysis"* variable Studiendauer (24 weeks: n= 1097 (45%); 36 weeks: n=547 (22%), 52 weeks: n=550 (23%)) gepoolte Analyse: *"Because the step-down closed-testing hierachrchy was broken here, all subsequent analyses were considered descriptive and not controlled for multiplicity"* **Registereintrag:** https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2016-001304-37-PL Kein direkter Vergleich: Dreifach-Fixkombination mit einer open label Dreifach-Kombi → für Einschätzung daher hinten angestellt

Zitat	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Kommentar
		· FF/UMEC/VI (200/31.25/25) µg vs. FF/VI (200/25) µg - rate ratio 1,08 (0,82; 1,42) · FF/UMEC/VI (200/62.5/25) µg vs. FF/VI (200/25) µg - rate ratio 0,97 (0,73;1,28) **Mean Change From Baseline in Asthma Control Questionnaire-7 (ACQ-7) Total Score at Week 24** gepoolte Interventionsgruppen + gepoolte Vergleichsgruppen: · FF/UMEC/VI (UMEC 31.25 µg) vs. FF/VI: - OR 1,15 (0,94; 1,42) · FF/UMEC/VI (UMEC 62.5 µg) vs. FF/VI: - OR 1,43 (1,16; 1,76) **Mean Change From Baseline in Saint George's Respiratory Questionnaire (SGRQ) Total Score at Week 24** gepoolte Interventionsgruppen + gepoolte Vergleichsgruppen: · FF/UMEC/VI (UMEC 31.25 µg) vs. FF/VI: - OR 0,86 (0,69; 1,06) · FF/UMEC/VI (UMEC 62.5 µg) vs. FF/VI: - OR 1,14 (0,92; 1,42)		

2.3.5 Preisvergleich LAMA/LABA/ICS-Fixkombination vs. lose Kombinationen

Diese Aufstellung wurde von Vertretenden der Arzneimittelkommission der Deutschen Apotheker (AMK) für die NVL Asthma (Version 5) orientierend erstellt.

- Zugrunde gelegt wurden die AVP des / der Originatorpräparate (keine Importe) jeweils auf Basis der größten verordnungsfähigen (= preis wertesten) O.P.
- Anforderung: Bei loser Kombination ICS nicht mono, sondern als LABA-ICS-Fixkombination.
- Bewertet wurden die Preise sowie ferner Adhärenz-relevante Aspekte (Anzahl eingesetzter Devices? verschiedene Device-Gruppen?; Stand 07/2022)

Mometasonfuroat + Indacaterol + Glycopyrronium

Dreierfixkombination: Enerzair® Breezhaler (Pulver)

Zusammensetzung	Dosierung	Preis	Tagesverordnungskosten
Mometasonfuroat (160) 136 µg Indacaterol-Acet. (150) 114 µg Glycopyrronium-Br (50) 46 µg	1 x 1 Kapsel tgl.	3 x 30 Kps. = € 268.90	€ 2.99 / Tag

Lose Kombination: ICS-LABA Atectura® 125/127.5 Breezhaler (Pulver) + SAMA Seebri 44 Breezhaler (Pulver) = identischer Pulverinhalator (nur 1 Device-Typ)

(Es gibt keine identisch zusammengesetzte Zweierkombination mit derselben Freisetzungsrate!)

Zusammensetzung	Dosierung	Preis	Tagesverordnungskosten
Mometasonfuroat (160) 127.5 µg Indacaterol-Acetat (150) 125 µg [Atectura]	1 x 1 Kapsel tgl	3 x 30 Kps. = € 111,76	€ 1.24 / Tag
Glycopyrronium-Br (50) 44 µg [Seebri]	1 x 1 Kapsel tgl.	3 x 30 Kps. = € 180.51	€ 2.01 / Tag
			€ 3.25 / Tag

Expert*inneneinschätzung:

Durch die lose Kombination erhöhen sich die Tagestherapiekosten um € 0.26 / Tag (8.7%)

Anzahl Tagesdosen: 1 (Enerzair®) vs. 2 (lose Kombi)

Beclometason-Dipropionat + Formoterol + Glycopyrronium

Beclometason-Dipropionat + Formoterol + Glycopyrronium

Dreierfixkombination: Trimbow® (Dosieraerosol, Lösung)

Zusammensetzung	Dosierung	Preis	Tagesverordnungskosten
Beclometason-DP (100) 87 µg Formoterol-hemifumarat (6) 5 µg Glycopyrronium-Br (12.5) 9 µg	2 x 2 Hübe tgl	3 x 120 Hübe = € 268.49	€ 2.98 / Tag

Lose Kombination: ICS-LABA Foster® / Inuvair 100/6 (Dosieraersol, Lsg. bzw. Pulverhinahaltor Foster® Nexthaler®) + Seebri 44 Breezhaler (Pulver) = 2 verschiedene Devices (bei Kombination DA und Pulver zwei Device-Gruppen mit abweichendem Inspirationsmuster)

Zusammensetzung	Dosierung	Preis	Tagesverordnungskosten
Beclometason-DP (100) 100 µg Formoterol-hemifumarat (6) 4.91 µg [Foster]	2 x 1-2 Hübe tgl. Für Preisvergleich 2 x 2 zugrunde gelegt	2 x 120 Hübe = € 108.54 (Preise von DA / Pulver identisch)	€ 1.81 / Tag
Glycopyrronium-Br (50) 44 µg [Seebri]	1 x 1 Kapsel tgl.	3 x 30 Kps. = € 180.51	€ 2.01 / Tag
			€ 3.82 / Tag

Expert*inneneinschätzung:

Durch die lose Kombination erhöhen sich die Tagestherapiekosten um € 0.84 / Tag (28.2 %)

Anzahl Tagesdosen: 4 (Trimbow®) vs. 5 (lose Kombi)

Fluticasonfuroat + Vilanterol + Umeclidinium

Dreierfixkombination: Elebrato® / Trelegy® Ellipta (Pulverinhalator)

Zusammensetzung	Dosierung	Preis	Tagesverordnungskosten
Fluticasonfuorat (100) 92 µg Vilanterol-trifenatat (25) 22 µg Umeclidinium-Br (74.15) 55 µg	1 x 1 Dosis tgl.	3 x 30 Dosen = € 216.23	€ 2.40 / Tag

Lose Kombination: ICS-LABA Revinty® / Relvar® (Pulverinhalator Ellipta) + Incruse® 55 / Rolufta® 55 (Pulverinhalator Ellipta) = identischer Pulverinhalator (nur 1 Devicetyp)

Zusammensetzung	Dosierung	Preis	Tagesverordnungskosten
Fluticasonfuorat (100) 92 µg Vilanterol-trifenatat (25) 22 µg [Relvar®]	1 x 1 Dosis tgl.	3 x 30 Dosen = € 105.29	€ 1.17 / Tag
Umeclidinium-Br (74.15) 55 µg [Rolufta®]	1 x 1 Dosis tgl.	3 x 30 Dosen = € 118.20	€ 1.31 / Tag
			€ 2.48 / Tag

Expert*inneneinschätzung:

Durch die lose Kombination erhöhen sich die Tagestherapiekosten um € 0.08 / Tag (3.3 %)

Anzahl Tagesdosen: 1 (Elebrato®/Trelegy®) vs. 2 (lose Kombi)

2.4 Dupilumab

Zitat	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
Bacharier LB, Maspero JF, Katelaris CH, et al. Dupilumab in Children with Uncontrolled Moderate-to-Severe Asthma. N Engl J Med 2021; 385(24):2230–40. DOI: 10.1056/NEJMoa2106567. http://www.ncbi.nlm.nih.gov/pubmed/34879449.	**VOYAGE** **Studiendesign:** phase 3, randomized, double-blind, placebo-controlled trial, 52 weeks **Population:** · children (age 6 - 11) with uncontrolled moderate-to-severe asthma (n=408) · receive a stable dose of standard background therapy (Medium-dose ICS with a second controller medication (i.e., LABA, LTRA, LAMA, or methylxanthines) or High-dose ICS alone or High-dose ICS with a second controller) **Intervention:** subcutaneous injection of dupilumab (dose of 100 mg for those weighing ≤30 kg; 200 mg for those weighing >30 kg) every 2 weeks **Vergleich:** matched placebo every 2	**Baseline-Patientencharakteristika:** · hinsichtlich Alter, Geschlecht, Gewicht weitestgehend ausgeglichen · (leicht) höhere Baseline-Werte in Dupilumab vs. Placebogruppen (wenn je nach efficacy populations unterteilt) hinsichtlich Blood eosinophil counts; IgE, FeNO --> signifikant? Use of high-dose inhaled glucocorticoid — no. (%) at baseline Patients with Type 2 Inflammatory Phenotype - Placebo (N = 114): 50 (43.9%) - Dupilumab (N = 236): 102 (43.2%) Patients with ≥300 Blood Eosinophils per mm^3 - Placebo (N = 84): 41 (48.8%) - Dupilumab (N = 175): 74 (42.3%) **Primary end point: annualized rate of severe asthma exacerbations** population type 2 inflammatory phenotype · 0.31 (95% CI 0.22; 0.42) in the dupilumab group and 0.75 (95% CI, 0.54;1.03) in the placebo group · relative risk reduction in the dupilumab group: 59.3% (95% CI 39.5;72.6)	**Selection bias** Randomisierung: low Allocation concealment: low **Performance bias** Verblindung von Teilnehmern und Personal: low **Detection bias** Verblindung der Ergebnisevaluation: unclear **Attrition bias** Verlust von Studienteilnehmern/ fehlende Daten: unclear ITT-Analyse: durchgeführt	**moderat** 1) Verzerrungsrisiko (RoB-Bewertung): -0,5 2) Direktheit/Übertragbarkeit auf Fragestellung: -0,5: (ggf. Abstufung: siehe Nutzenbewertung des G-BA --> zweckmäßige Vergleichstherapie einer patientenindividuellen Therapieeskalation nicht umgesetzt)	Daten für Kinder ab 6 Jahren Beachten: Einschätzung zur zweckmäßigen Vergleichsintervention des G-BA (Nutzenbewertung und Beschluss: https://www.g-ba.de/downloads/39-261-5645/2022-10-06_AM-RL-XII_Dupilumab_D-804_BAnz.pdf https://www.g-ba.de/downloads/92-975-5683/2022-04-

Zitat	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
	weeks **Follow up**: 12 weeks of post-treatment **relevantes Ausschlusskriterium:** Patients requiring a third controller medication for their asthma were not considered eligible for this study **Definition "primary efficacy populations":** · either a type 2 inflammatory asthma phenotype (≥150 blood eosinophils per cubic millimeter or a fraction of exhaled nitric oxide of ≥20 ppb at baseline) or · a blood eosinophil count of at least 300 cells per cubic millimeter at baseline	population with at least 300 eosinophils per cubic millimeter at baseline · 0.24 (95% CI, 0.16; 0.35) in the dupilumab group and 0.67 (95% CI, 0.47; 0.95) in the placebo group · relative risk reduction: 64.7% (95% CI, 43.8; 77.8) patients with at least 150 eosinophils per cubic millimeter at baseline · relative reduction in the risk of severe exacerbations with dupilumab, as compared with placebo: 61.0% (95% CI, 41.7; 73.9) patients with a FeNO of at least 20 ppb at baseline · relative reduction in the risk of severe exacerbations 61.6% (95% CI, 35.1;77.3) all the patients who had undergone randomization · relative reduction in the risk of severe exacerbations 54.2% (95% CI, 32.9; 68.7) among **Sicherheit:** Adverse events: siehe Tabelle 2 der Publikation	**Reporting bias** selektive Ergebnisdarstellung: low **Andere Biasursachen** Baseline imbalance: unclear/high Interessenkonflikte/ Sponsoring: Sanofi and Regeneron Pharmaceuticals		15_Nutzenbewertung-IQWiG_Dupilumab-D-804.pdf
Wechsler ME, Ford LB, Maspero JF, et al. Long-term safety and efficacy of dupilumab in patients with moderate-to-severe asthma (TRAVERSE): An open-label extension study. Lancet Respir Med 2022; 10(1):11–25. DOI: 10.1016/S2213-2600(21)00322-	**TRAVERSE** **Studiendesign:** open-label, multicentre, single-arm, extension study **Population:** adults and adolescents (aged 12-84 years) with moderate-to-severe or oral-corticosteroid-dependent severe asthma who had completed a previous dupilumab asthma study (phase 2A EXPEDITION, phase 2B DRI [P2b], phase 3 QUEST, or VENTURE) **Intervention inkl. Dosierung und Schema** - dupilumab 300 mg every 2 weeks up to 96 weeks **Definition der Gruppen:** Treatment in patients who received placebo in the	safety data are presented for all enrolled patients who were exposed to dupilumab from each of the four parent studies: n = 2282 (78,1%; median age 50 years, 62 ,1% female and 37, 9% male) - 2062 patients with non-OCSdependent moderate-to-severe asthma from P2b (placebo-dupilumab, lll of 158 induded in the parent study; dupilumab-dupilumab, 421 of 611) and QUEST (placebo-dupilumab, 517 of 638; dupilumab-dupilumab, 1013 of 1264); - 33 patients with moderate-to-severe asthma from EXPEDITION (placebo-dupilumab, 19 of 22; dupilumab-dupilumab, 14 of 20); - and 187 patients with OCS-dependent severe asthma from VENTURE (placebo-dupilumab, 97 of 107; dupilumab-dupilumab, 90 of 103) > Overall, 2182 (95,6%) of 2282 patients completed TRAVERSE to week 48 and 1240 (54,3%) patients to week 96 **primärer Endpunkt: any treatment emergent adverse event** up to		1) Verzerrungsrisiko (RoB-Bewertung): -1 2) Präzision (Fallzahl, Eventzahl, KI-Weite): +/-0 3) Direktheit/Übertragbarkeit: -1 (wenige Kinder, keine Kontrollintervention; Einschluss wegen Sicherheitshinweise)	TRAVERSE Extension Studie zu Asthma Liberty Venture and Asthma Liberty Quest --> beide Studien in NVL Asthma 4. Aufl. beschrieben >> single-arm-Studie (Dupilumab): wegen potentieller Sicherheitshinweise dennoch eingeschlossen

Zitat	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
2. http://www.ncbi.nlm.nih.gov/pubmed/34597534.	parent study and were exposed to dupilumab in TRAVERSE is referred to as placebo-dupilumab, while treatment in patients who received dupilumab in both studies is referred to as dupilumab-dupilumab. **Behandlungsdauer:** defined as exposure to dupilumab during the TRAVERSE study unless otherwise stated; owing to an amendment during the conduct of the study, this duration could be up to 48 weeks or 96 weeks **Studienzeitraum:** 08/2014 - 10/2019 - 362 hospitals and clinical centres across 27 countries	week 96 (or week 48 for patients enrolled after the protocol amendment). - ranged from 76,3% to 94,7% (similar to that observed in the parent studies) - The most frequently reported treatment-emergent adverse events were nasopharyngitis (17,5-25,9%), injection-site erythema (2,2-23,4%), and bronchitis (9,3-19,0%). - Serious asthma exacerbations (0,5-3,6%) and pneumonia (0,7-2,7%) were the most frequently reported serious adverse events. - There were four treatment-emergent adverse events leading to death.			
EUCTR2022-002375-11-Outside-EU/EEA. Efficacy and Safety Study of Dupilumab in Patients with Persistent Asthma. https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2022-002375-11-Outside-EU/EEA 2022.	Adults and adolescent patients (≥12 years of age) **Primary Objective:** To evaluate the efficacy of dupilumab in patients with persistent asthma > The study was conducted at 65 active sites in China and India. **Intervention:** Dupilumab - 200 mg (175 mg per millilitres [mg/mL] in 1.14 mL) or Dupilumab 300 mg (150 mg/mL in 2 mL) SC injection q2w for 24 weeks. Loading dose - Subjects without oral corticosteroids (OCS) maintenance therapy received dupilumab 400 milligrams (mg) loading dose (2 doses of 200 mg) subcutaneous (SC) injection on Day 1 (Week 0) followed by dupilumab 200 mg SC injection every 2 weeks (q2w) for 24	Children (2-11 years): 0 Adolescents (12-17 years): 1 Adults (18-64 years): 419 From 65 to 84 years: 66 85 years and over: 0 **Resultate hier:** https://www.clinicaltrialsregister.eu/ctr-search/trial/2022-002375-11/results		/	Adults and adolescent patients (≥12 years of age) **Primary Objective:** To evaluate the efficacy of dupilumab in patients with persistent asthma **Secondary Objectives:** To evaluate the safety and tolerability of dupilumab To evaluate the effect of dupilumab on improving patient reported outcomes including health related quality of life

Zitat	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
	weeks. - Subjects on OCS maintenance therapy received dupilumab 600 mg loading dose (2 doses of 300 mg) SC injection on Day 1 (Week 0) followed by dupilumab 300 mg SC injection q2w for 24 weeks. **Vergleich:** Placebo				To evaluate dupilumab systemic exposure and immunogenicity > The study was conducted at 65 active sites in China and India. clinicaltrials.gov: https://clinicaltrials.gov/ct2/show/NCT03782532 **>> Asiatische Kohorte**

Nutzenbewertungen/Sicherheitsdaten

Die Nutzenbewertung des G-BA findet sich unter folgendem Link: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/820/

Die EMA-Dokumente zu Dupixent können Sie hier einsehen: https://www.ema.europa.eu/en/medicines/human/EPAR/dupixent

2.5 Tezepelumab

Evidenzbericht

SR: Es konnten keine geeigneten systematischen Übersichtsarbeiten identifiziert werden. Insbesondere aufgrund methodischer Mängel wurden thematisch passende Übersichtsarbeiten im Volltext-Screening ausgeschlossen. Alle RCTs, welche in den Übersichtsarbeiten betrachtet wurden, wurden in dieser Recherche zu Tezepelumab ebenfalls identifiziert.

RCT: Es wurden alle Hauptstudien identifiziert, welche auch vom G-BA betrachtet wurden (NAVIGATOR, SOURCE, DESTINATION). Die Phase II-Studie PATHWAY wurde ebenfalls identifiziert und extrahiert, jedoch als Ez (zurückgestellt) gewertet, da die Folge-Phase III-Studie NAVIGATOR bereits eingeschlossen wurde.

Zitat	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
Menzies-Gow A. Tezepelumab in Adults and	**NAVIGATOR:** asthma exacerbation study **Studiendesign**	**Baseline-Patientencharakteristika (relevante)** - *mean blood eosinophil count* höher in der Placebo-Gruppe: Tezepelumab 327±293 cells/µl vs. Placebo 353±488 cells/µl	**Selection bias** Randomisierung: **low**	Erwachsene: **niedrig** Jugendliche: **sehr niedrig**	

Zitat	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
Adolescents with Severe, Uncontrolled Asthma. N Engl J Med 2021; 384(19):1800–9. https://www.ncbi.nlm.nih.gov/pubmed/33979488.	-phase 3, multicenter, randomized, double-blind, placebo controlled trial **Population** -patients with severe, uncontrolled asthma (12 to 80 years of age); n = 1061 **Intervention** - tezepelumab (210 mg) subcutaneously every 4 weeks for 52 weeks (n = 529) **Vergleich** - placebo subcutaneously every 4 weeks for 52 weeks (n = 532) **Follow-up** - at week 52, patients entered a 12-week post-treatment follow-up period or the long-term extension study (DESTINATION) **relevante Einschlusskriterien** - received medium or high-dose inhaled glucocorticoids (daily dose of ≥500 µg of fluticasone propionate or equivalent) for at least 12 months before screening and at least one additional controller medication, with or without oral glucocorticoids, for at least 3 months before the date of informed consent. - morning prebronchodilator FEV1: < 80% of the predicted normal value (<90% for patients 12 to 17 years of age) during the run-in period. - Postbronchodilator (albuterol) FEV1 reversibility of at least 12% and at least 200 ml: documented during the 12 months before screening or during the run-in period. - at least two asthma exacerbations (defined for trial eligibility and end-point	(in randomisierten Gruppen nach Median (range), ≥ oder < 300 cells/µl ausgeglichen verteilt) + - *mean serum total IgE* höher in Placebo-Gruppe: Tezepelumab 515.7±959.8 IU/ml vs. Placebo 614.1±1159.5 IU/ml (in randomisierten Gruppen nach Median (range) ausgeglichen verteilt) - andere Baseline-Charakteristika weitestgehend ausgeglichen **Additional maintenance treatments (in addition to ICS) at baseline:** no. (%) Tezepelumab / Placebo / Total LABA: 259 (49.1) / 267 (50.3) / 526 (49.7) LABA and LTRA: 133 (25.2) / 130 (24.5) / 263 (24.8) LABA, LAMA, and LTRA: 73 (13.8) / 59 (11.1) / 132 (12.5) LABA and LAMA: 59 (11.2) / 66 (12.4) / 125 (11.8) LAMA: 1 (0.2) / 1 (0.2) / 2 (0.2) LTRA: 0 (0.0) / 3 (0.6) / 3 (0.3) **primärer Endpunkt: annualized rate of asthma exacerbations** - tezepelumab: 0.93 (95% CI, 0.80 to 1.07) - placebo: 2.10 (95% CI, 1.84 to 2.39) - rate ratio, 0.44; 95% CI, 0.37 to 0.53 **annualized rate of asthma exacerbations in patients with baseline blood eosinophil counts of < 300 cells/µl:** - tezepelumab: 1.02 (95% CI, 0.84 to 1.23) - placebo: 1.73 (95% CI, 1.46 to 2.05) - rate ratio, 0.59; 95% CI, 0.46 to 0.75 **sekundäre Endpunkte (Auswahl)** At week 52, improvements were greater with tezepelumab than with placebo - ACQ-6 (−1.55 vs. −1.22; difference, −0.33; 95% CI, −0.46 to −0.20) - AQLQ (1.49 vs. 1.15; difference, 0.34; 95% CI, 0.20 to 0.47) - ASD (−0.71 vs. −0.59; difference, −0.12; 95% CI, −0.19 to −0.04). **AEs** The frequencies and types of adverse events did not differ meaningfully between the two groups. **SAEs** Signal bei *Cardiac disorders:* Tezepelumab n= 5 (0.9%); Placebo n= 1 (0.2%)	Allocation concealment: **unclear** **Performance bias** Verblindung von Teilnehmern und Personal: **low** **Detection bias** Verblindung der Ergebnisevaluation: **unclear** **Attrition bias** Verlust von Studienteilnehmern/ fehlende Daten: **low** **Reporting bias** selektive Ergebnisdarstellung: **low** **Andere Biasursachen high** Baseline imbalance: Unterschiede in Mean blood eosinophil count + mean serum total IgE: unclear	1) Verzerrungsrisiko: -1 (insbesondere durch "andere Biasursachen") 2) Präzision - Erwachsene: +/-0 - Jugendliche: -1 (Fallzahl gering (n=82/1061; 7,7%)) 3) Direktheit/Übertragbarkeit: -1 (Angemessenheit der Kontrollintervention: eingeschränkt: Es fand keine Anpassung bzw. mögliche Eskalation der vorhandenen medikamentösen Therapie während der gesamten Studiendauer statt. Nach NVL Stufenschema kommen sowohl für Erwachsene, als auch für Ki/Jug. andere Möglichkeiten der Therapieeskalation vorab noch in Betracht)	

Zitat	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
	measures as a worsening of asthma symptoms that led to hospitalization, an emergency department visit that resulted in the use of systemic glucocorticoids for ≥3 consecutive days, or the use of systemic glucocorticoids for ≥3 consecutive days) in the 12 months before the date of informed consent. **Studienzeitraum:** 11/ 2017 - 9/2020 **Ort:** at 297 sites in 18 countries **Messmethoden** - Asthma Control Questionnaire–6 (ACQ-6; range, 0 [no impairment] to 6 [maximum impairment]) - Asthma Quality of Life Questionnaire (AQLQ; range, 1 [maximum impairment] to 7 [no impairment]) - Asthma Symptom Diary (ASD; range, 0 [no symptoms] to 4 [worst possible symptoms]).		Interessenkonflikte/ Sponsoring: Funded by AstraZeneca and Amgen; einige Autoren bekommen Gelder von verschiedenen Pharmafirmen (darunter Erstautor z.B: von AstraZeneca); medical writer auch von AstraZeneca finanziert: high multiples Testen: hierarchisch getestet;angegebene Endpunkte laut statist. Analyseplan = konfirmatorisch finales Studienprotokoll von: Date 14 May 2020 (ca 4 Monate vor Studienende)		
Wechsler ME. Evaluation of the oral corticosteroid-sparing effect of	**SOURCE:** aims to evaluate the oral corticosteroid-sparing potential of tezepelumab **Studiendesign:** phase III, multicentre,	**Baseline-Patientencharakteristika (relevante)** - alle Teilnehmer*innen: LABA + ICS Additional maintenance treatments (in addition to ICS) LAMA: 34 (46%) tezepelumab group vs. 40 (53%) placebo group LTRA: 30 (41%) tezepelumab group vs. 36 (47%) placebo group	**Selection bias** Randomisierung (Generierung): **low**	**niedrig** 1) Verzerrungsrisiko: -0,5	

Zitat	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
tezepelumab in adults with oral corticosteroid-dependent asthma (SOURCE): A randomised, placebo-controlled, phase 3 study. Lancet Respir Med 2022; 10(7):650–60. https://www.ncbi.nlm.nih.gov/pubmed/35364018	randomised, double-blind, placebo-controlled study **Population:** adults with oral corticosteroid-dependent asthma; aged 18-80 years **vor Randomisation:** - Patients who were receiving medium-dose inhaled corticosteroids must have had their dose increased to a high dose for at least 3 months before screening. - After an oral corticosteroid optimisation phase of up to 8 weeks, participants were randomly assigned [...]At the end of the optimisation phase, particpants eligible for randomisation must have had a final oral corticosteroid dose of between 7,5 mg and 30 mg. **Intervention inkl. Dosierung und Schema** Tezepelumab 210 mg subcutaneously every 4 weeks during a 48 week treatment period (4 week induction phase, 36 week oral corticosteroid reduction phase, and 8 week maintenance phase) **Vergleich** Placebo **oral corticosteroid reduction phase** As in the optimisation phase, daily oral corticosteroid doses of 10 mg or less were reduced by 2,5 mg, and doses of greater than 10 mg were reduced by 5 mg. **relevante Einschlusskriterien** - physician-diagnosed asthma, receiving medium-dose (daily dose 250 -	- leichte Unterschiede in Verteilung auf verschiedene cuttoffs bei: blood eosinophils, FeNO, perennial allergen-specific IgE status; ansonsten Baseline-Charakteristika weitestgehend ausgeglichen **primary endpoint:** categorised percentage reduction from baseline in daily oral corticosteroid dose at week 48 without the loss of asthma control The cumulative odds of achieving a category of greater percentage reduction in an oral corticosteroid dose for daily maintenance at week 48 were similar with tezepelumab or placebo in the overall population (OR 1,28 [95% CI 0,69-2,35]; the primary endpoint was not met). - reduction of their daily oral corticosteroid dose by 90-100%: 40/74 (54%) participants in the tezepelumab group vs. 35/76 (46%) participants in the placebo group - reduction 75% - <90%: 5/74 (7%) vs. 4/76 (5%) - reduction 50% - <75%: 10/74 (14%) vs. 14/76 (18%) - reduction 0% - <50%: 5/74 (7%) vs. 9/76 (12%) The cumulative odds were higher with tezepelumab than with placebo in participants with baseline blood eosinophil counts of at least 150 cells per µL (OR 2,58 [1,16-5,75]), but not in participants with counts below 150 cells per µL (OR 0,40 [0,14-1,13]). --> siehe Figure 3 im VT **Sicherheit** Tezepelumab was well tolerated, with no safety concerns identified. 53 (72%) of 74 tezepelumab-assigned participants and 65 (86%) of 76 placebo-assigned participants reported an adverse event. Serious adverse events were reported in 12 (16%) participants in the tezepelumab group and 16 (21%) participants in the placebo group. E**xacerbations** Of participants who completed the planned treatment period, a higher proportion of participants in the tezepelumab group (35 [47%] of 74) had no exacerbations during the planned treatment period than those in the placebo group (26 [34%] of 76). In the time to first exacerbation analysis, there was a delayed separation of the treatment groups starting at approximately day 168 (hazard ratio [HR] 0,74 [95% CI 0,48-1,15]; an HR of less than 1 favours tezepelumab: appendix p 6). The rate of exacerbations associated with an emergency department visit or hospitalisation was 0,16 (95% CI 0, 06-0,44) in the tezepelumab group and 0,28 (0,13-0,58) in the placebo group (RR 0,59 [0,19-1,82). **authors conclusion:** " We did not observe a significant improvement in oral corticosteroid dose reduction with tezepelumab versus placebo in the overall population	**Allocation concealment** verdeckte Zuteilung: **low** **Performance bias** Verblindung von Teilnehmern und Personal: **low** **Detection bias** (Verblindung der Ergebnisevaluation): **unclear** Sponsor? **Attrition bias:** Verlust von Studienteilnehmern/ fehlende Daten: **low** ITT-Analyse: nein **Reporting bias** selektive Ergebnisdarstellung: **low** **andere Biasursachen: high** Baseline imbalance: **unclear** Interessenkonflikte/ Sponsoring: **high** The funders of the study	2) Präzision: -0,5 (weite Konfidenzintervalle) 3) Direktheit/Übertragbarkeit: -1 (Vergleichstherapie: nur jeweils ca 1/3 der Teilnehmer*innen hat noch ein 3. Medikament zur Langzeittherapie eingenommen (LAMA oder LTRA))	

Zitat	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
	500µg fluticasone propionate or equivalent) or high-dose (daily dose >500µg) inhaled corticosteroids and had at least one asthma exacerbation in the 12 months before screening - must have receiving LABA with or without additional medication for at least 3 month before screening - must have receiving oral corticosteroids for the treatment of asthma for at least 6 month before screening and must have been taking a stable dose of prednisone or prednisolone 7,5 - 30 mg daily or daily equivalent for at least 1 month before screening - morning pre-BD FEV1 < 80%predicted - Additional maintenance asthma controller medications were permitted if participants used them according to standard-of-care practice and if use of these medications was documented for at least 3 months before screening. **Studienzeitraum:** 05/2018 - 09/2019 - across 60 sites in seven countries	of this oral corticosteroid-sparing study, although an improvement was observed in participants with baseline blood eosinophil counts of at least 150 cells per µL."	(AstraZeneca and Amgen) contributed to the study design and data interpretation. The study sponsor (AstraZeneca) conducted the study, coordinated the data management and did the statistical analysis in collaboration with investigators at the academic centres.		
Menzies-Gow A. Long-term safety and efficacy of tezepelumab in people with severe, uncontrolled asthma (DESTINATION): A randomised, placebo-con-	**DESTINATION** **Studiendesign**: phase 3, multicentre, randomised, double-blind, placebo-controlled, long-term extension study **Population:** recruited from NAVIGATOR and SOURCE **Intervention inkl. Dosierung und Schema** subcutaneous tezepelumab (210 mg every 4 weeks **Vergleich** placebo (every 4 weeks)	Baseline-Patientencharakteristika (relevante): siehe SOURCE und NAVIGATOR **primary endpoints**: exposure-adjusted incidence of adverse events For individuals who initially received tezepelumab (n=528) in NAVIGATOR, incidence of adverse events over 104 weeks was 49,62 (95% CI 45,16 to 54,39) per 100 patient-years, compared with 62,66 (56,93 to 68,81) for those receiving placebo (n=531; difference -13·04; 95% CI -17,83 to -8,18) In SOURCE, incidence of adverse events was 47,15 (36,06 to 60,56) per 100 patient-years for those who initially received tezepelumab (n=74) and 69,97 (54,54 to 88,40) for those who received placebo (n=76; difference -22,82; -34,77 to -10,01). serious adverse events NAVIGATOR: For serious adverse events, incidence was 7,85 (6,14 to 9,89) per	**Selection bias** Randomisierung (Generierung): **low** **Allocation concealment** (verdeckte Zuteilung): **low** **Performance bias (**Verblindung von Teilnehmern und Personal):	**moderat** (Aussagen zur Sicherheit) 1) Verzerrungsrisiko: -0,5 2) Präzision: +/-0 ausreichend 3) Direktheit/Übertragbarkeit: -0,5 (Angemessenheit der Kontrollintervention: Siehe Einschätzungen	The reason for this imbalance in cardiac serious adverse events is not understood. There is no known biological mechanism by which

Zitat	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
trolled extension study. Lancet Respir Med 2023; 11(5):425–38. https://www.ncbi.nlm.nih.gov/pubmed/36702146.	**Randomisation**: 3:1 (tezepelumab to placebo) Those who were previously randomised to receive tezepelumab in either parent study continued treatment of subcutaneous tezepelumab (210 mg every 4 weeks); those who were previously randomised to receive placebo in either parent study were re-randomised 1:1 to receive either subcutaneous tezepelumab (210 mg every 4 weeks) or placebo (every 4 weeks) **Studiendauer:** Total treatment duration (including the parent studies) was 104 weeks for all groups **Follow-Up:** 12 weeks **relevante Einschlusskriterien** - Participants (aged 12-80 years) were required to have good treatment compliance in the parent study. **Studienzeitraum:** recruited 01/2019 - 10/2021 - across 182 sites (including hospitals, clinics, medical centres, clinical trial centres, and private practices) in 18 countries	100 patient-years for individuals who initially received tezepelumab and 12,45 (9,97 to 15,35) for those who received placebo (difference -4,59; -7,69 to -1,65) SOURCE: For serious adverse events, incidence was 13,14 (7,65 to 21,04) per 100 patient-years for those who initially received tezepelumab and 17,99 (10,66 to 28,44) for those who received placebo (difference -4,85; -14,88 to 4,53). The incidence per 100 patient-years of respiratory, thoracic, and mediastinal serious adverse events was lower in those receiving tezepelumab than in those receiving placebo, while the incidence of cardiac-serious adverse events was higher in those receiving tezepelumab than those receiving placebo. The incidence of cardiac adverse events, independently adjudicated major adverse cardiovascular events and cardiovascular deaths was similar in tezepelumab and placebo recipients. Serious cardiac events will continue to be assessed in-ongoing and future studies. **secondary endpoint:** annualised asthma exacerbation rate Tezepelumab reduced the annualised asthma exacerbation rate over 104 weeks compared with placebo. In participants initially from NAVIGATOR, the annualised asthma exacerbation rate ratio over 104 weeks was 0,42 (95% CI 0,35 to 0,51); in those initially from SOURCE, the ratio over 104 weeks was 0,61 (0,38 to 0,96).	**low** **Detection bias** (Verblindung der Ergebnisevaluation): **unclear** (Sponsor?: Analyses will be performed by AstraZeneca or its representatives) **Attrition bias:** Verlust von Studienteilnehmern/ fehlende Daten: **low** ITT-Analyse: nein **Reporting bias** (selektive Ergebnisdarstellung): **low** **andere Biasursachen: high** Baseline imbalance: **unclear** Interessenkonflikte/ Sponsoring: **high** FUNDING: AstraZeneca and Amgen: The funders of the study, AstraZeneca and Amgen, contributed to the study design and data	der Komtrollintervention bei SOURCE und NAVIGATOR)	blocking TSLP with tezepelumab would lead to cardiac pathophysiology, and the very low expression ofTSLP and TSLP receptor mRNA in cardiac tissue suggests that signalling via the TSLP receptor pathway in these tissues is unlikely.

Zitat	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
			interpretation, and funded medical writing support for this manuscript. The study sponsor, AstraZeneca, did the study, coordinated the data management, and did the statistical analysis in collaboration with investigators at the academic centres, all of whom had access to the final study data. ; potentielle IK der Autoren		

Nutzenbewertungen/Sicherheitsdaten

Die Nutzenbewertung des G-BA findet sich unter folgendem Link: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/904/

Die EMA-Dokumente zu Tezspire können Sie hier einsehen: https://www.ema.europa.eu/en/medicines/human/EPAR/tezspire

2.6 Selektiv eingebrachte Literatur

Zitat	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
Melén E, Nwaru BI, Wiklund F, et al. Short-acting β 2 -	**Studiendesign:** population-based cohort study (Swedish national healthcare registries)	Gesamt: 219,561 patients - Analytical outcomes were assessed for 1 and 3 years of follow-up. As children can outgrow their asthma, the 1-year follow-up was considered for primary analysis.	(In Anlehnung an NOS) **I. Selektion der Studienteilnehmer** Verzerrungsrisiko: niedrig **II. Vergleichbarkeit**	**Aussagesicherheit: niedrig** Ausgangspunkt: Studiendesign - niedrig – Beobachtungsstudie	

Zitat	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
agonist use and asthma exacerbations in Swedish children: A SABINA Junior study. Pediatr Allergy Immunol. 2022; 33(11):e13885. DOI: 10.1111/pai.13885. https://pubmed.ncbi.nlm.nih.gov/36433853/	**Population:** patients with asthma (<18 years) treated in secondary care between 2006–2015 **Outcome:** Exacerbation risk, by baseline SABA collection (0–2 vs. ≥3 canisters, further examined as ordinal/continuous variable) - stratified on comorbid atopic disease (allergic rhinitis, dermatitis and eczema, and food/other allergies) - assessed for 1-year follow-up using negative binomial regression Definition asthma exacerbations: hospitalization, emergency room (ER) visit due to asthma, or an oral corticosteroid (OCS) claim for asthma treatment **Studienzeitraum:** 2006 - 2015; Schweden	**collected ≥3 SABA canisters during the baseline year (high use):** - age 0–5: 45.4% - age 6-11: 31.7% - age 12-17: 26.5% Collection of ≥3 SABA canisters (vs. 0–2) was associated with increased exacerbation risk during follow-up (incidence rate ratio): - 0-5-: 1,35 (95%CI 1,29; 1,42) - 6-11: 1,22 (95% CI 1,15; 1,29) - 12-17: 1,26 (95% CI 1,19; 1,34) - the association persisted with SABA as a continuous variable and was stronger among patients without atopic diseases (32%–44% increased risk versus. 14%–21% for those with atopic disease across groups).	Verzerrungsrisiko: niedrig **III. Endpunkterfassung** Verzerrungsrisiko: niedrig **IV. Col/ Funding**: funded by AstraZeneca, Erst- und Letztautor auch personal fees from AstraZeneca	1) Verzerrungsrisiko (RoB-Bewertung): gering; jedoch potentiellen Einfluss Sponsor beachten: +/-0 2) Präzision (sehr große Fallzahl, enge Konfidenzintervalle): +/-0 3) Direktheit/Übertragbarkeit auf Fragestellung: ausreichend gut: +/-0	
Vogelberg C, Engel M, Laki I, et al. Tiotropium add-on therapy improves lung function in children with symptomatic moderate asthma. J Allergy Clin Immunol Pract 2018; 6(6):2160-2162.e9. DOI:	**Phase-III-Studie (CanoTinA-asthma)** **Design/ Intervention:** Randomized, Parallel Assignment, Double-Blind • Experimental: tiotropium high dose QD Once daily, • Experimental: tiotropium low dose QD Once daily, • Placebo Comparator: placebo QD Once daily **Follow-up:** k.A. (min 48 Wo) **Population:** randomisiert: n= 403 **Einschlusskriterien (ausgewählt):** • 6-11y • 6-month history of asthma • treatment with ICS (stable medium dose), either as mono or in combination with another controller,(at least 4 weeks before Visit1) • LABAs are not permitted • be symptomatic (partly controlled) ACQ-IA mean score ≥ 1.5 • bronchodilator reversibility: ≥12%, 15 to 30	**Clinical trials (NCT01634139)** **Baseline-Patientencharakteristika:** Alter ausgeglichen, Geschlecht nicht ausgeglichen **Primäre EP** (at week 24): • Placebo vs R2.5: MD 0.170, 95%KI 0,108; 0.231 • Placebo vs. R5: MD 0,614, 95%KI 0,103; 0.255 **sekundäre EP** (at week; ausgewählt): ACQ−IA Total Score (Weeks 24) • Placebo vs R2.5: MD -0.120, 95%KI -0,262; 0.022 • Placebo vs. R5: MD -0,182, 95%KI -0.323; -0.041 ACQ−IA Total Score (Weeks 48) • Placebo vs R2.5: MD -0.065, 95%KI -0,208; 0.078 • Placebo vs. R5: MD -0,093, 95%KI -0.236; 0.049 PAQLQ(S) Total Score Weeks 24 • Placebo vs R2.5: MD 0.176, 95%KI 0.035; 0.316	**Selection bias** Randomisierung: low (pseudo-random number generator with a supplied seed number) Allocation concealment: low **Performance bias** Verblindung von Teilnehmern und Personal: low **Detection bias** Verblindung der Ergebnisevaluation: unklar **Attrition bias** Verlust von Studienteilnehmern/ fehlende Daten: teilweise unklar ITT: high (as treated) **Reporting bias** selektive Ergebnisdarstellung: unklar Andere Biasursachen Baseline imbalance: low	1) Verzerrungsrisiko (RoB-Bewertung): -1 (unklar, Einfluss Sponsor beachten) 2) Präzision: -0,5 3) Direktheit/Übertragbarkeit auf Fragestellung: +/-0	Primären EP im Studienverlauf erweitert Siehe auch Leitlinienreport, NVL Asthma 4. Auflage [8] Für Version 5 der NVL ist nun einePublikation der Studie vorhanden (via "Clinical Communications" veröffentlicht), daher Bewertung der Verzerrungsrisiken

Zitat	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
10.1016/j.jaip.2018.04.032 https://pubmed.ncbi.nlm.nih.gov/29751157/	minutes after 200 mcg salbutamol/albuterol • able to use the Respimat inhaler, trial related procedures **Ausschlusskriterien (ausgewählt):** • schwere andere Erkrankung, Herzerkrankungen, Malignome, Tbc, narrow-angle glaucoma • abnormal screening haematology or blood chemistry • renal impairment, as defined by a creatinine clearance <50 mL/min/1.73 m2 BSA • treated with anti-IgE (prior 6 mo), Beta-Blocker (prior 4 mo), theophylline (2/4 Wo)	• Placebo vs. R5: MD 0.127, 95%KI -0.013; 0.267 PAQLQ(S) Total Score Weeks 48 • Placebo vs R2.5: MD -0.021, 95%KI -0.163 to 0.120 • Placebo vs. R5: MD 0.017, 95%KI -0.124 to 0.158 **Sicherheit** (ausgewählt): SAE: • Placebo: 6/131 (4,58%); R2.5: 3/135 (2,22%); R5: 1/135 (0,74%) AE: • Placebo: 79/131 (60,31%); R2.5: 76/135 (56,3%); R5: 71/135 (52,59%) **Publikation:** The number of asthma worsening was lower in both tiotropium groups compared with placebo. The number of patients reporting asthma worsening during the 48-week treatment period was 57 (42.2%) for tiotropium 5 mg, 63 (46.7%) for tiotropium 2.5 mg, and 65 (50.4%) for placebo. Severe exacerbations were reported at similar frequencies in all 3 treatment groups during the treatment period (7 patients each [5.2%] in the tiotropium 5 and 2.5 mg groups, and 6 patients [4.6%] in the placebo group).	Interessenkonflikte/ Sponsoring: Boehringer Ingelheim, Pfizer		auf Bassis dessen durchgeführt

2.7 Weitere Literatur

Zitat	Charakteristika des SR	Kommentar
Undela K. Macrolides versus placebo for chronic asthma. Cochrane Database Syst Rev 2021; 11(11):CD002997. https://www.ncbi.nlm.nih.gov/pubmed/34807989	**Fragestellung:** To assess the effects of macrolides compared with placebo for managing chronic asthma.	nicht zitiert, da Thema nicht in NVL adressiert
Naing C. Statins for asthma. Cochrane Database Syst Rev 2020; 7(7):CD013268.	**Fragestellung:** To assess the benefits and harms of statins as an adjunct therapy for asthma in adults and children.	nicht zitiert, da Thema nicht in NVL adressiert

Zitat	Charakteristika des SR	Kommentar
https://www.ncbi.nlm.nih.gov/pubmed/32668027. 2020		
Daley-Yates PT. Inhaled Corticosteroids. Potency, dose equivalence and therapeutic index. Clin Pharmacol 2015; 80(3):372-80 https://pubmed.ncbi.nlm.nih.gov/25808113/	Referenz: Therapeutische Indices	Conflicts of interest: Peter Daley-Yates ist Mitarbeiter und Shareholder von Glaxo Smith Kline (Hersteller von Fluticason-propionat und Fluticason-furoat-haltigen AM).

3 Evidenztabellen Nicht-Medikamentöse Therapie

3.1 Selbstmanagement

Zitat	Charakteristika des SR	Ergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
Harris K. School-based self-management interventions for asthma in children and adolescents: A mixed methods systematic review. Cochrane Database Syst Rev 2019; 1(1):CD011651. https://www.ncbi.nlm.nih.gov/pubmed/30687940	**Fragestellung:** (1) To identify the intervention features that are aligned with successful intervention implementation. (2) To assess effectiveness of school-based interventions provided to improve asthma self-management among children. **Suchzeitraum:** latest search on 28 August 2017 **Population:** school-aged children with asthma who received the intervention in school **Setting:** primary/elementary schools through to high/senior schools **Intervention:** asthma self-management interventions delivered at school **Control:** usual care or a self-management or health intervention with a focus other than asthma (placebo) **primäre Endpunkte:** • Asthma symptoms or exacerbations leading to	> school-based self-management interventions compared with no intervention <u>Exacerbations leading to hospitalisation (hospitalisations)</u> - probably reduce mean hospitalisations by an average of about 0.16 admissions per child over 12 months SMD –0,19 (95% KI -0,35; -0,04); I² = 0%, 6 RCTs, n = 1873, Aussagesicherheit moderat <u>Asthma symptoms leading to emergency hospital visits (ED visits)</u> -may reduce number of children who visit EDs from 7.5% to 5.4% over 12 months: OR 0,70 (95% KI 0,53; 0,92); I² = 25,76%, 13 RCTs, n = 3883, Aussagesicherheit niedrig <u>Unplanned visit to hospital or GP due to asthma symptoms (unplanned medical visits)</u> - probably reduce unplanned visits to hospitals or primary care from 26% to 21% at 6 to 9 months OR 0,74 (95% KI 0,60; 0,90); I² = 0%, 5 RCTs, n = 3490, Aussagesicherheit moderat	AMSTAR2: Qualität des Reviews: - **high** AMSTAR-Score kritische Kriterien: 7/7	siehe endpunktspezifische GRADE-Bewertung des Reviews	

Zitat	Charakteristika des SR	Ergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
	admission to hospital (children with one or more admissions or high admission rates) • Asthma symptoms or exacerbations leading to emergency department visits • Parent-reported absence from school • Days of restricted activity **Body of evidence:** (1) n = 33 studies in 14,174 children provided information for the QCA (2) n = 33 RCTs in 12,623 children measured the effects of interventions	<u>Experience of daytime symptoms</u> - SMD -0.15 (95% KI -0,33;0,02); I² = 0%, 5 RCTs, n = 1065, Aussagesicherheit na <u>Experience of night-time symptoms</u> - SMD -0,18 (95% KI -0,52; 0,15), I² = 40,14%, 4 RCTs, n = 459, Aussagesicherheit moderat <u>Days of restricted activity</u> - Self-management interventions probably reduce the number of days of restricted activity by just under half a day over a two-week period MD 0,38 Tage (95% KI -0,41; -0,18); I² = 0%, 3 RCTs, n = 1852, Aussagesicherheit moderat <u>Absence from school</u> - Effects of interventions on school absence are uncertain due to the variation between the results of the studies MD 0.4 fewer school days missed per year with self-management (95% KI -1,25; 0,45); I² = 70,09%, 10 RCTs, n = 4609, Aussagesicherheit niedrig <u>Use of reliever therapies, e.g. beta2-agonists (reliever therapies)</u> - Evidence is insufficient to show whether the requirement for reliever medications is affected by these interventions OR 0,52 (95% KI 0,15; 1,81); I² = 67,53%, 2 RCTs, n = 437, Aussagesicherheit sehr niedrig <u>Health-related quality of life</u> - Self-management interventions probably improve children's asthma-related quality of life by a small amount MD 0,36 units higher on the Paediatric AQLQ (95% KI 0,06; 0,64); I² = 81,24%, 7 RCTs, n = 2587, Aussagesicherheit moderat			

3.2 Atemphysiotherapie

Zitat	Charakteristika des SR	Ergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
Santino TA. Breathing exercises for adults with asthma. Cochrane Database Syst Rev 2020; 3(3):CD001277. https://www.ncbi.nlm.nih.gov/pubmed/32212422	**Fragestellung:** To evaluate the evidence for the efficacy of breathing exercises in the management of people with asthma **Suchzeitraum:** latest search was on 4 April 2019 **Population:** adults with asthma **Intervention:** breathing exercises **Control:** control group receiving asthma education or, alternatively, with no active control group **primärer Endpunkt:** Quality of life **Body of Evidence:** 22 studies involving 2880 participants	**Breathing exercises versus inactive control** Asthma Quality of Life Questionnaire (AQLQ) - improvement favouring the breathing exercises group - at three months: MD 0,42 (95% KI 0,17; 0,68); I² =76,01%, 4 Studien, n = 974, Aussagesicherheit moderat - at six months: OR 1,34 (95% KI 0,97; 1,86); 1 Studie, n = 655, Aussagesicherheit na) for the proportion of people with at least 0,5 unit improvement in AQLQ asthma symptoms: Asthma Control Questionnaire (ACQ) - up to three months = inconclusive - MD -0,15 units (95% KI −2,32; 2,02); 1 Studie, n=115, Aussagesicherheit niedrig - similar over six months: MD −0,08 units (95% KI −0,22; 0,07); 1 Studie, n = 449, Aussagesicherheit na) hyperventilation symptoms: Nijmegen Questionnaire - from four to six months: meta-analysis showed less symptoms with breathing exercises (MD −3,22, 95% KI −6,31; −0,13); I² = 0%, 2 Studien, n = 118, Aussagesicherheit moderat), but this was not shown at six months (MD 0,63 (95% KI −0,90; 2,17); I² = 14,54%, 2 studies, n = 521, Aussagesicherheit na). **Breathing exercises versus asthma education** quality of life - one study measuring AQLQ was inconclusive up to three months (MD 0.04, 95% CI -0.26 to 0.34; 1 study, 183 participants). - when assessed from four to six months, the results favoured breathing exercises (MD 0.38, 95% CI 0.08 to 0.68; 1 study, 183 participants). Hyperventilation symptoms: Nijmegen Questionnaire - inconclusive up to three months: MD −1,24 (95% KI −3,23; 0,75); 1 Studie, n =183, Aussagesicherheit na) - favoured breathing exercises from four to six months: MD −3,16 (95% KI −5,35; −0,97); 1 Studie, n = 183, Aussagesicherheit na)	AMSTAR2: Qualität des Reviews: - **low** AMSTAR-Score kritische Kriterien: 6/7 PY=1 - Kein Protocoll einsehbar; differences between Protocol and Review jedoch im Text beschrieben	siehe endpunktspezifische GRADE-Bewertung des Reviews	Update von Freitas DA, Holloway EA, Bruno SS, et al. Breathing exercises for adults with asthma. (Kapitel 6.4 Atemphysiotherapie; NVL Asthma 4. Auflage) > nine new studies (1910 participants) in this Update

3.3 Apps zur Asthmatherapie

Zitat	Charakteristika des SR	Ergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
Chan A. Digital interventions to improve adherence to maintenance medication in asthma. Cochrane Database Syst Rev 2022; 6(6):CD013030. https://www.ncbi.nlm.nih.gov/pubmed/35691614.	**Allgemeine Angaben:** Metaanalyse (RCTs including cluster- and quasi-randomised trials) **Fragestellung:** To determine the effectiveness of digital interventions for improving adherence to maintenance treatments in asthma. **Suchzeitraum:** October 2021 **Population:** adults and children with asthma (n = 15207) **Intervention:** digital adherence intervention **Control:** non-digital adherence intervention or usual care **Outcome (Auswahl):** · adherence (16 studies) · asthma control (16 studies) · asthma exacerbations (6 studies) · unscheduled healthcare utilisation (4 studies) · lung function (7 studies) · quality of life (10 studies)	**digital interventions including:** · interactive voice response (IVR) calls (n = 2) · speech recognition (n = 2) · electronic monitoring devices (n = 10) · web-based interventions (n = 10) · mobile applications (n = 7) · SMS-based interventions (n = 12) · videobased (n = 2) · MP3-player (n = 1) · medication dispensing system (n = 1) · audiotape (n = 1) **Adherence** (% of people adhering to their prescribed medication): · digital adherence interventions: MD 14.66 higher (95% KI 7,74; 21,57); I² = 94%, 16 RCTs; n= 8885, **GRADE: LOW** · subgroups: -- electro medical devices (EMDs): 22,5 MD (95% KI 10,84; 34,16); I² = 92%, 7 RCTs, n = 932 -- SMS: 12,12 MD (95% KI 6,22; 18,03); I² = 24%, 4 RCTs, n = 391 **Asthma control** - change from baseline (various scales; higher scores = better asthma control) · The mean change from baseline in asthma control in the intervention group compared to the control group was an increase: 0.31 SD higher (95%KI 0,17; 0,44); I² = 35%, 15 RCTs, n= 1638; **GRADE: MODERATE** **Asthma exacerbations** - Number of people with one or more exacerbations · 105/1000 vs. 198/1000; RR 0,53 (95%KI 0,32; 0,91); I² = 37%, 6 RCTs, n = 678; **GRADE: LOW** **Unscheduled healthcare utilisation** - number of hospital or GP/ED visits · 147/1000 vs. 199/1000; RR 0,74 (95%KI 0,51; 1,06); I² = 0%; 4 RCTs, n = 446; **GRADE: LOW**	AMSTAR2 Qualität des Reviews: **high** AMSTAR-Score kritische Kriterien: 7/7	siehe endpunktspezifische GRADE-Bewertung des Reviews	confidence in the evidence was reduced by risk of bias and inconsistency

Zitat	Charakteristika des SR	Ergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
		Quality of life - change from baseline (various scales; higher scores indicate better quality of life) · The mean change from baseline in quality of life score was an increase: 0.26 SD higher (95%KI 0,07; 0.45), I² = 38%, 10 RCTs, n = 848; **GRADE: MODERATE** > für detaillierte Auswertungen; u.a. nach einzelnen digitalen Device-Typen: siehe Tabellen *Comparison 1. Digital intervention versus usual care* (S. 117 ff); *Comparison 2. Digital intervention versus usual care - sensitivity analyses* (S. 133 ff)			

4 Evidenztabellen Asthmaanfall bei Erwachsenen/Kindern und Jugendlichen

4.1 Stabile vs. erhöhte ICS-Dosis

Zitat	Charakteristika des SR	Ergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
Kew KM. Increased versus stable doses of inhaled corticosteroids for exacerbations of chronic asthma in adults and children. Cochrane Database Syst Rev 2022; 9(9):CD007524.	**Fragestellung:** To compare the clinical effectiveness and safety of increased versus stable doses of ICS as part of a patient-initiated action plan for the home management of exacerbations in children and adults with persistent asthma. **Suchzeitraum:** to 20 December 2021 **Population:** children and adults with persistent asthma (mild to moderate) **Intervention**: blinded inhaler in the event of an exacerbation which increased their daily dose of ICS **Control:** blinded inhaler in the event of an exacerbation which kept daily dose of ICS stable (placebo) **Body of evidence:** 9 RCTs	**Treatment failure: need for systemic corticosteroids (ITT)** - increased dose of ICS vs. Placebo: OR 0.97, (95% CI 0.76 to 1.25; 8 studies; 1774 participants; I² = 0%; moderate quality evidence) - Results for the same outcome in the subset of participants who initiated the study inhaler were unchanged from the previous version: OR 0.84, 95% CI 0.54 to 1.30; 7 studies; 766 participants; I2 = 42%; very low confidence - subgroup children: OR 1.07 [0.76 , 1.49]; I² = 10%, 4 studies, keine Fallzahl angegeben, Aussagesicherheit na) Pooled effects for - unscheduled physician visits (142/1000 vs. 147/1000; OR 0.96 (0.66 to 1.41), n = 931, 3 RCTs, GRADE: low) - unscheduled acute care 12/1000 vs. 23/1000; POR 0.50 (0.16 to 1.56), n = 704, 4 RTCs, GRADE: very low)	AMSTAR2: Qualität des Reviews: - **high** AMSTAR-Score kritische Kriterien: 7/7	siehe endpunktspezifische GRADE-Bewertung des Reviews	Update zu 231. Kew KM, Quinn M, Quon BS, et al. Increased versus stable doses of inhaled corticosteroids for exacerbations of chronic asthma in adults and children. Cochrane Database Syst Rev 2016(6):CD007524. DOI: 10.1002/14651858.CD007524.pub4. http://www.ncbi.nlm.nih.gov/pubmed/27272563.

Zitat	Charakteristika des SR	Ergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
https://www.ncbi.nlm.nih.gov/pubmed/36161875	(1923 participants; 7 parallel and 2 cross-over) - 5 studies evaluated adult populations (n = 1247; ≥ 15 years), - 4 studies evaluated child or adolescent populations (n = 676; < 15 years).	- emergency department or - hospital visits, and - duration of exacerbation made it very difficult to determine where the true effect may lie, and confidence was reduced by risk of bias. **serious adverse events** - favoured keeping ICS stable - OR 1.69, 95% CI 0.77 to 3.71; 2 studies; 394 participants; I^2 = 0%, GRADE: very low **non-serious adverse events** - favoured keeping ICS stable - OR 2.15, 95% CI 0.68 to 6.73; 2 studies; 142 participants; I^2 = 0%, GRADE: very low			

4.2 Zusammenfassung verschiedener Cochrane-Reviews

Zitat	Charakteristika des SR	Kommentar
Craig SS. Interventions for escalation of therapy for acute exacerbations of asthma in children: An overview of Cochrane Reviews. Cochrane Database Syst Rev 2020; 8(8):CD012977. https://www.ncbi.nlm.nih.gov/pubmed/32767571	**Fragestellung:** To summarise Cochrane Reviews with or without meta-analyses of randomised controlled trials on the efficacy and safety of second-line treatment for children with acute exacerbations of asthma (i.e. after first-line treatments, titrated oxygen delivery, and administration of intermittent inhaled short-acting beta2-agonists and oral corticosteroids have been tried and have failed)	Alle in dieser Übersicht eingeschlossenen Cochrane-Reviews wurden auch für die NVL Asthma identifiziert, bewertet und entsprechend der jeweiligen Fragestellung bereits inkludiert <u>eingeschlossene Cochrane-Reviews:</u> - Camargo 2003 - Griffiths 2013 - Vezina 2014 - Knightly 2017 - Normansell 2018 - Mitra 2005 - Travers 2012 a - Travers 2012 b - Griffiths 2016 - Rodrigo 2006 (für 3. Auflg. NVL Asthma identifiziert; nicht zitiert; PICO) - Watts 2012 (für 4. Auflg. NVL Asthma identifiziert; nicht zitiert; PICO) - Korang 2016 (für 4. Auflg. NVL Asthma identifiziert; nicht zitiert; PICO) siehe Leitlinienreport zur 3. Auflage [11]; siehe Leitlinienreport zur 4. Auflage [8]

5 Evidenztabelle Asthma mit Arbeitsplatzbezug

5.1 Interventionen am Arbeitsplatz

Zitat	Charakteristika desSR	Ergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
Henneberger PK. Workplace interventions for treatment of occupational asthma. Cochrane Database Syst Rev 2019; 10(10):CD006308. https://www.ncbi.nlm.nih.gov/pubmed/31593318	**Fragestellung:** To evaluate the effectiveness of workplace interventions on occupational asthma. **Suchzeitraum:** up to July 31, 2019 **Population:** workers of all genders - with asthma and a work-related pattern of symptoms, pulmonary function changes, immunological or inflammatory changes, and/or changes in airway hyperreactivity, such that occupational asthma was considered to be the most likely diagnosis by their treating physician **Intervention/Control:** - complete removal from exposure and/or - reduced exposure vs. - continued exposure - complete removal from exposure vs. - reduced exposure **Body of Evidence:** 26 non-randomized controlled before and after studies, n = 1,695 participants	**removal from exposure vs. continued exposure** - Removal may increase the likelihood of reporting absence of asthma symptoms (269/1000 vs. 56/1999; RR 4.80 (95% CI 1.67 to 13.86), I^2 = 66.89%, n = 641, 9 studies; GRADE: very low) - may improve asthma symptoms (351/1000 vs. 142/1000; RR 2.47 (95% CI 1.26 to 4.84), I^2 = 67.37%, n = 435, 9 studies, GRADE: very low) - non-specific bronchial hyperreactivity (NSBH) may improve with removal from exposure (SMD 0.43 (95% CI 0.03 to 0.82); I^2 = 63.68%, n = 387, 6 studies, GRADE: very low) **reduction of exposure vs. continued exposure** - Reduction of exposure may increase the likelihood of reporting absence of symptoms (95/1000 vs. 36/1000; RR 2.65 (95% CI 1.24 to 5.68), I^2 = 0%, n = 334, 7 studies, GRADE: very low) **removal from exposure vs. reduction of exposure** - no increase in the likelihood of reporting absence of symptoms (770/1000 vs. 127/1000; RR 6.05 (95% CI 0.86 to 42.34); I^2 = 81.82%, n = 359, 6 studies, GRADE: very low) - no improvement in symptoms (931/1999 vs. 839/1000; RR1.11 (95% CI 0.84 to 1.47); I^2 = 60.62%, n = 140, 5 studies, GRADE: very low) - there may be improved results for removal from exposure in the subset of patients exposed to low molecular weight agents **risk of unemployment** - risk of unemployment after removal from exposure may increase compared with reduction of exposure (510/1000 vs. 36/1000; RR 14.28 (95% CI 2.06 to 99.16); I^2 = 0%, n = 64, 2 studies, GRADE: very low) - 4 studies reported a decrease in income of 20% to 50% after removal from exposure	AMSTAR2: Qualität des Reviews: - **high** AMSTAR-Score kritische Kriterien: 7/7	siehe endpunktspezifische GRADE-Bewertung des Reviews	Update zu Groene 2011 (in 4. Auflage zitiert) - 5 zusätzliche Studien identifiziert

6 Evidenztabelle Rehabilitation

6.1 Pulmonale Rehabilitation

Zitat	Charakteristika desSR	Ergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
Osadnik CR. Pulmonary rehabilitation versus usual care for adults with asthma. Cochrane Database Syst Rev 2022; 8(8):CD013485. https://www.ncbi.nlm.nih.gov/pubmed/35993916	**Fragestellung:** To evaluate, in adults with asthma, the effectiveness of pulmonary rehabilitation compared to usual care on exercise performance, asthma control, and quality of life (co-primary outcomes), incidence of severe asthma exacerbations/ hospitalisations, mental health, muscle strength, physical activity levels, inflammatory biomarkers, and adverse events. **Suchzeitraum:** May 2021 **Population**: adults with asthma; mean age range 27 to 54 years. **Intervention:** pulmonary rehabilitation **Control**: usual care **Body of evidence:** 10 studies; n = 894 participants (range 24 to 412 participants (n = 2 studies involving n > 100, one contributing to metaanalysis)	**Pulmonary rehabilitation:** - Most programmes were outpatientbased, lasting from 3-4 weeks (inpatient) or 8-12 weeks (outpatient) - Education or self-management components included breathing retraining and relaxation, nutritional advice and psychological counselling - 1 programme was specifically tailored for people with severe asthma **Pulmonary rehabilitation vs. usual care** - evidence is very uncertain about the effects on incremental shuttle walk test distance (MD between groups 74.0 metres, 95% CI 26.4 to 121.4; 1 study; n = 30, GRADE: very low). - likely improves functional exercise capacity as measured by 6-minute walk distance (MD 79.8 metres; 95% CI 66.5 to 93.1; 5 studies; n = 529; moderate certainty evidence; I^2 = 0%). - evidence is very uncertain about the longer-term effects one year after pulmonary rehabilitation for this outcome (MD 52.29 metres, 95% CI 0.7 to 103.88; 2 studies; n = 42, GRADE: very low, I^2 = 72%) - may result in a small improvement in asthma control compared to usual care as measured by Asthma Control Questionnaire (ACQ) (MD between groups of −0.46 (95% CI −0.76 to −0.17; 2 studies; n = 93; low certainty evidence; I^2 = 0%); - data derived from the Asthma Control Test were very uncertain (MD between groups 3.34, 95% CI −2.32 to 9.01; 2 studies; n = 442; I^2 = 91%). - Pulmonary rehabilitation results in little to no difference in asthma control as measured by ACQ at nine to 12 months follow-up (MD 0.09, 95% CI −0.35 to 0.53; 2 studies; n = 48; low certainty evidence; I^2 = 0%). - likely results in a large improvement in quality of life as assessed by the St George's Respiratory Questionnaire	AMSTAR2: Qualität des Reviews: - **high** AMSTAR-Score kritische Kriterien: 7/7	siehe endpunktspezifische GRADE-Bewertung des Reviews	´- Primärstudien: Nathell, Cambach, Schultz auch in NVL Asthma inkludiert

Zitat	Charakteristika desSR	Ergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
		(SGRQ) total score (MD −18.51, 95% CI −20.77 to −16.25; 2 studies; n = 440; moderate certainty evidence; I^2 = 0%), - may have little to no effect on Asthma Quality of Life Questionnaire (AQLQ) total scores, with the evidence being very uncertain (MD 0.87, 95% CI −0.13 to 1.86; 2 studies; n = 442, GRADE: very low; I^2 = 88%). - Longer-term follow-up data suggested improvements in quality of life may occur as measured by SGRQ (MD −13.4, 95% CI −15.93 to −10.88; 2 studies; n = 430, GRADE: very low, I^2 = 98%) but not AQLQ (MD 0.58, 95% CI −0.23 to 1.38; 2 studies; n = 435; GARE: very low, I^2 = 78%); however, the evidence is very uncertain			

7 Evidenztabelle Komplementäre und alternative Therapie

7.1 Vitamin D

Zitat	Charakteristika des SR	Ergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
Williamson A. Vitamin D for the management of asthma. Cochrane Database Syst Rev 2023; 2(2):CD011511. 10.1002/14651858.CD011511.pub3 https://pubmed.ncbi.nlm.nih.gov/36744416/	**Suchzeitraum:** 09/2022 **Fragestellung:** To evaluate the effectiveness and safety of administration of vitamin D or its hydroxylated metabolites in reducing the risk of severe asthma exacerbations (defined as those requiring treatment with systemic corticosteroids) and improving asthma symptom control. **Population:** - children and adults with a clinical diagnosis of asthma, based on the presence of characteristic symptoms and signs (i.e. wheeze, shortness of breath, chest tightness, or cough), variable airflow obstruction, or both	**Allgemeines:** - majority mild/moderate, minority severe asthma - all but two studies investigated effects of administering cholecalciferol (vitamin D3) - profound vitamin D deficiency (25-hydroxyvitamin D (25(OH)D) < 25 nmol/L) at baseline was rare **Vitamin D vs. Placebo** asthma exacerbations treated with systemic corticosteroids Administration of vitamin D or its hydroxylated metabolites did not reduce or increase the proportion of participants experiencing one or more asthma exacerbations treated with systemic corticosteroids - 226/1000 vs. 219/1000; OR 1,04 (95% KI 0,81; 1,34), I^2 = 0%; 14 RCTs, n = 1778, **GRADE: high** rate of exacerbations requiring systemic corticosteroids no effect of vitamin D supplementation on the rate of exacerbations requiring systemic corticosteroids - rate ratio 0,86 (95% KI 0,62; 1,19); I^2 = 60%, 10 studies, n = 1599; **GRADE: high**	AMSTAR2: Qualität des Reviews: - high AMSTAR-Score kritische Kriterien: 7/7	siehe GRADE-Bewertungen im Ergebnisteil	Aussage zum Nutzen/zur Wirkung von Vitamin D im Vergleich zur Vorversion (2016) verändert (siehe Leitlinienreport zur 4. Auflage [8]) Review nach Ende des Suchzeitraums für strukturierte Recherche veröffentlicht

Zitat	Charakteristika des SR	Ergebnisse	Methodische Qualität	Aussagesicherheit der Evidenz	Kommentar
	- no restrictions regarding disease severity, baseline vitamin D status, or duration of treatment with asthma medication **Intervention:** Vitamin D or its hydroxylated metabolites **Vergleich:** Placebo **Primärer Endpunkt:** asthma exacerbations treated with systemic corticosteroids **Body of Evidence:** 1155 children (15 Studies), 1070 adults (5 studies); total: 20 RCTs	time to first exacerbation no effect of the time to first exacerbation - hazard ratio 0,82 (95% KI 0,59; 1,15); I^2 = 22%; 3 studies, n = 850; **GRADE: high** exacerbations requiring emergency department visit or hospitalisation, or both Administration of vitamin D did not reduce or increase the proportion of participants experiencing at least one asthma exacerbation precipitating an emergency department visit or hospital admission, or both - 46/1000 vs. 79/1000; OR 0,56 (95% KI 0,26; 1,21); I^2 = 33%, 9 RCTs, n = 1070; **GRADE: moderate** end-study ACT - MD 0,23 higher in vitamin D arm (95% KI -0,26; 0,73); I^2 = 29%; 7 studies, n = 1271; **GRADE: moderate** SAEs - 49/1000 vs. 55/1000; OR 0,89 (95% KI 0,56; 1,41); I^2 = 0%; 12 studies, n = 1556, **GRADE: high** fatal asthma exazerbation - 90/1000 vs. 86/1000; risk difference 0,00 (95% KI -0,01; 0,01); I^2 = 0%; 16 studies, n = 1976, **GRADE: low** Subgroup analysis did not reveal any evidence of effect modification by baseline vitamin D status, vitamin D dose, frequency of dosing regimen, or age. A single trial investigating administration of calcidiol reported a benefit of the intervention for the primary outcome of asthma control. **Forschungs bzw. Evaluationsbedarf:** Further research is required to clarify potential effects of calcidiol on risk of asthma exacerbation, and to determine whether vitamin D supplementation may yet have an effect in people with severe asthma or those with the lowest levels of baseline vitamin D (25(OH)D < 25 nmol/L), in whom a significant protective effect cannot currently be excluded.			

8 Versorgungskoordination

8.1 Gezielte Recherche

Zitat	Typ
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8.2 Weitere Literatur

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