Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2018-B-107-z Benralizumab

Stand: Mai 2018

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Benralizumab bei schwerem eosinophilem Asthma	
Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*Siehe Übersicht II*. Zugelassene Arzneimittel im Anwendungsgebiet
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Nicht angezeigt
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschluss des G-BA über eine Änderung der Arzneimittel-Richtlinie (AM-RL): - Mepolizumab (Anlage XII – Nutzenbewertung nach §35a SGB V, Beschluss vom 21. Juli 2016) - Reslizumab (Anlage XII – Nutzenbewertung nach §35a SGB V, Beschluss vom 6. Juli 2017) Beschluss des G-BA über eine Änderung der Arzneimittel-Richtlinie (AM-RL) - Anlage IV: - Therapiehinweis zu Omalizumab (Beschluss vom 17. Dezember 2015) DMP-Richtlinie (DMP-RL): Asthma
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe Evidenzsynopse*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Benralizumab R03DX10 Fasenra®	„Add-On-Erhaltungstherapie bei erwachsenen Patienten mit schwerem eosinophilem Asthma, das trotz hochdosierter inhalativer Kortikosteroide plus langwirksamer Beta-Agonisten unzureichend kontrolliert ist (siehe Abschnitt 5.1b).“
Beta-2-Sympathomimetika (inhalativ; kurzwirkend) (SABA)	
Salbutamol R03AC02 Salbutamol CT	Zur Verhütung und Behandlung von Atemwegserkrankungen mit reversibler Obstruktion, wie z. B. Asthma bronchiale oder chronische Bronchitis. Hinweis: Eine längerfristige Behandlung soll symptomorientiert und nur in Verbindung mit einer entzündungshemmenden Dauertherapie erfolgen. (FI Salbutamol CT, Stand 04/2015)
Fenoterol R03AC04 Berotec N®	- Symptomatische Behandlung von akuten Asthmaanfällen. - Prophylaxe von belastungsinduziertem Asthma bronchiale. - Symptomatische Behandlung von Asthma bronchiale allergischer und nichtallergischer Ursache und/oder anderen Erkrankungen, die mit einer reversiblen Obstruktion der Atemwege einhergehen, z.B. chronisch obstruktive Bronchitis mit und ohne Lungenemphysem. Hinweis: - Sofern eine Dauerbehandlung erforderlich ist, soll stets eine begleitende antiinflammatorische Therapie erfolgen. (FI Berotec, Stand 09/2015)
Beta-2-Sympathomimetika (systemisch; kurzwirkend) (SABA)	
Reproterol R03CC14 Bronchospasmin	Zur kurzfristigen Behandlung des schweren bronchospastischen Anfalls und des Status asthmaticus. (FI Bronchospasmin, Stand 02/2016)

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Beta-2-Sympathomimetika (inhalativ; langwirkend) (LABA)	
Salmeterol R03AC12 Serevent®	Zur Langzeitbehandlung von Atemwegserkrankungen mit Verengung der Atemwege durch Krämpfe der Bronchialmuskulatur (obstruktive Atemwegserkrankungen), wie z. B. Asthma bronchiale (anfallsweise auftretende Atemnot durch Atemwegsverkrampfung, insbesondere nächtliches Asthma), chronische Bronchitis und Blählunge (Lungenemphysem). Gleichzeitig soll beim Asthma bronchiale eine regelmäßige Therapie mit entzündungshemmenden Arzneimitteln (inhalative und/ oder orale Kortikoide) sichergestellt werden, da Serevent kein Ersatz hierfür ist. Diese Behandlung mit Kortikoiden ist regelmäßig weiterzuführen. Warnhinweis: Serevent Dosier-Aerosol und Serevent Diskus sollen nicht für die Akutbehandlung eines Asthmaanfalls eingesetzt werden. (FI Serevent ® Dosier-Aerosol, Stand 02/2015)
Formoterol R03AC13 Formoterol CT	- Symptomatische Langzeitbehandlung des chronischen mäßigen bis schweren Asthma bronchiale in Kombination mit einer entzündungshemmenden Dauertherapie (z. B. Kortikosteroide). - […] Hinweis: Bisher liegen keine Hinweise darauf vor, dass Formoterol eine Behandlung mit Kortikosteroiden ersetzen kann. Bei Asthma bronchiale muss Formoterol in jedem Fall mit Kortikosteroiden zur Inhalation kombiniert werden. (FI Formoterol-CT, Stand 06/2015)
Beta-2-Sympathomimetika (oral; kurz-, langwirkend)	
Terbutalin R03AC03 Aerodur Turbohaler®	Atemwegserkrankungen mit Verengung der Atemwege durch Krämpfe der Bronchialmuskulatur (obstruktive Atemwegserkrankungen), wie z.B. Asthma bronchiale, chronische Bronchitis und Blählunge (Lungenemphysem). (FI Aerodur Turbohaler, Stand 07/2015)
Salbutamol R03CC02 Salbubronch®	Verhütung und Behandlung von Atemwegserkrankungen bei Erwachsenen und Kindern ab 2 Monaten, die mit einer Verengung der Atemwege durch Krämpfe der Bronchialmuskulatur einhergehen (obstruktive Atemwegserkrankungen), wie z. B. bei Asthma bronchiale, chronischer Bronchitis und Blählunge (Lungenemphysem). Hinweis

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	SALBUBRONCH Elixier ist nur für Patienten, die nicht symptomorientiert mit inhalativen β2-Sympathomimetika behandelt werden können, geeignet. Eine Behandlung mit SALBUBRONCH Elixier sollte in Ergänzung zu einer entzündungshemmenden Dauertherapie mit Glukokortikoiden oder anderen entzündungshemmend wirkenden Substanzen erfolgen. (FI SALBUBRONCH® Elixier, Stand 02/2014)
Bambuterol R03CC12 Bambec®	Verhütung und Behandlung von Atemwegserkrankungen, die mit einer Verengung der Atemwege durch Krämpfe der Bronchialmuskulatur einhergehen (obstruktive Atemwegserkrankungen). Hinweis: Bambec ist nur für Patienten, die nicht symptomorientiert mit inhalativen Beta-2-Sympathomimetika behandelt werden können, geeignet. Bei Patienten mit Asthma bronchiale sollte eine Behandlung mit Bambuterol in Ergänzung zu einer entzündungshemmenden Dauertherapie, z. B. mit Glukokortikoiden zur Inhalation oder Leukotrien- Rezeptor-Antagonisten, erfolgen. (FI Bambec®, Stand 05/2016)
Clenbuterol R03CC13 Spiropent®	Symptomatische Behandlung chronisch obstruktiver Atemwegserkrankungen mit reversibler Atemwegsverengung, wie z. B. Asthma bronchiale oder chronisch obstruktive Bronchitis mit und ohne Emphysem. Hinweis Spiropent Tabletten sind nicht zur symptomorientierten Behandlung des akuten Asthmaanfalls geeignet. Eine Behandlung mit Spiropent Tabletten sollte in Ergänzung zu einer entzündungshemmenden Dauertherapie mit Kortikoiden oder anderen entzündungshemmend wirkenden Substanzen erfolgen. (FI Spiropent®, Stand 03/2014)
Clenbuterol/ Ambroxol R03CC63 Spasmo Mucosolvan Saft®	Akute und chronische Atemwegserkrankungen, die mit spastischen Verengungen, veränderter Sekretbildung und gestörtem Sekrettransport einhergehen, insbesondere spastische Bronchitiden, Emphysembronchitiden und Asthma bronchiale. Hinweis Spasmo-Mucosolvan Saft ist nicht zur symptomorientierten Behandlung des akuten Asthmaanfalls geeignet. Sofern eine Dauerbehandlung eines Asthma bronchiale mit Spasmo-Mucosolvan Saft erforderlich ist, soll stets eine begleitende antiinflammatorische Therapie (z. B. mit Kortikoiden) erfolgen. (FI Spasmo-Mucosolvan® Saft, Stand 03/2016)
Anticholinergika (inhalativ)	

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Tiotropiumbromid R03BB04 Spiriva® Respimat®	[…] Spiriva Respimat ist indiziert als ein zusätzlicher dauerhaft einzusetzender Bronchodilatator bei erwachsenen Asthma-Patienten, die als Dauertherapie eine Kombination aus inhalativen Kortikosteroiden (≥ 800 µg Budesonid/Tag oder Äquivalent) und langwirksamen Beta2-Agonisten erhalten, und die im Vorjahr mindestens eine schwere Exazerbation erfahren haben. (FI Spiriva® Respimat®, Stand 02/2016)
Inhalative Corticosteroide (ICS)	
Beclometason R03BA01 Junik®	zur Behandlung von Atemwegserkrankungen, wenn die Anwendung von Glukokortikoiden erforderlich ist, wie z.B. bei: Asthma bronchiale, chronisch obstruktiver Bronchitis […] (FI Junik®, Stand 03/2013)
Budesonid R03BA02 BUDECORT®	Zur Behandlung persistierender Atemwegserkrankungen, wenn die Anwendung von Glukokortikoiden erforderlich ist, wie z.B. bei: - Asthma bronchiale - Chronisch obstruktiver Bronchitis. (FI Budecort® 200 Novolizer®, Stand 06/2014)
Ciclesonid R03BA08 ALVESCO®	Zur Behandlung von persistierendem Asthma bei Erwachsenen und Jugendlichen (ab 12 Jahren). (FI Alvesco®, Stand 04/2016)
Fluticason R03BA05 FLUTIDE®	Dauerbehandlung eines persistierenden Asthma bronchiale aller Schweregrade. Hinweis: Fluticason-17-propionat ist nicht für die Akutbehandlung eines Asthmaanfalles geeignet. (FI Flutide®, Stand 07/2016)
Mometason R03BA07 ASMANEX®	Bei Erwachsenen und Jugendlichen ab 12 Jahren zur regelmäßigen Behandlung, um anhaltendes Asthma bronchiale zu kontrollieren. (FI ASMANEX® Twisthaler®, Stand 10/2014)

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Corticosteroide (systemisch, oral)	
Prednisolon, Prednisolon ratiopharm	[…] Asthma bronchiale (DS: c-a), gleichzeitig empfiehlt sich die Verabreichung von Bronchodilatatoren. (FI Prednisolon-ratiopharm, Stand 08/2010)
Prednison, Prednison ratiopharm	[…] Asthma bronchiale (DS: c-a), gleichzeitig empfiehlt sich die Verabreichung von Bronchodilatatoren. FI Prednison-ratiopharm, Stand 09/2011)
Weitere	
Theophyllin (systemisch) R03DA04 z.B. Theophyllin retard-ratiopharm	Bronchospasmolytikum/Antiasthmatikum Behandlung und Verhütung von Atemnotzuständen aufgrund von Verengung der Atemwege (Bronchokonstriktion) bei Patienten mit persistierendem Asthma bronchiale oder mittel- bis schwergradiger obstruktiver Atemwegserkrankung (z. B. chronische Bronchitis und Lungenemphysem). Hinweis: Es wird empfohlen die Dauertherapie dieser Erkrankungen mit Theophyllin in Kombination mit anderen die Bronchien erweiternden und entzündungshemmenden Arzneimitteln, wie z. B. lang wirksamen β-Sympathomimetika und Glukocortikoiden durchzuführen. Arzneimittel mit verzögerter Theophyllin- Freisetzung, wie Theophyllin retardratiopharm®, sind nicht zur Akutbehandlung des Status asthmaticus oder der akuten Bronchospastik bestimmt. Theophyllin sollte nicht als Mittel der ersten Wahl zur Behandlung von Asthma bei Kindern angewendet werden. (FI Theophyllin retard-ratiopharm, Stand 04/2014)
Omalizumab R03DX05 Xolair®	Xolair wird angewendet bei Erwachsenen, Jugendlichen und Kindern (6 bis < 12 Jahre). Die Behandlung mit Xolair sollte nur bei Patienten in Betracht gezogen werden, bei denen von einem IgE-(Immunglobulin E-) vermittelten Asthma ausgegangen werden kann (siehe Abschnitt 4.2). Erwachsene und Jugendliche (ab 12 Jahren) Xolair wird als Zusatztherapie zur verbesserten Asthmakontrolle bei Patienten mit schwerem persistierendem allergischem Asthma angewendet, die einen positiven Hauttest oder in vitro Reaktivität gegen ein ganzjährig auftretendes Aeroallergen zeigen und sowohl eine reduzierte Lungenfunktion (FEV1 < 80 %) haben als auch unter häufigen Symptomen während des Tages oder nächtlichem Erwachen leiden und trotz täglicher Therapie mit hoch dosierten inhalativen Kortikosteroiden und einem lang wirkenden inhalativen Beta2-Agonisten mehrfach dokumentierte, schwere Asthma-Exazerbationen hatten.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	(FI Xolair®, Stand 09/2016)
Mepolizumab R03DX09 Nucala®	Nucala ist angezeigt als Zusatzbehandlung bei schwerem refraktärem eosinophilem Asthma bei erwachsenen Patienten (siehe Abschnitt 5.1). (FI Nucala®, Stand 02/2017)
Reslizumab R03DX08 CINQAERO®	CINQAERO wird angewendet als Zusatztherapie bei erwachsenen Patienten mit schwerem eosinophilem Asthma, das trotz hochdosierter inhalativer Kortikosteroide plus einem anderen Arzneimittel zur Erhaltungstherapie nur unzureichend zu kontrollieren ist (siehe Abschnitt 5.1). (FI CINQAERO®, Stand 08/2016)
Kombinationspräparate (ICS/LABA)	
Beclometason/ Formoterol R03AK08 Foster®	Foster ist angezeigt für die regelmäßige Behandlung von Asthma, bei der die Anwendung eines Kombinationsprodukts (von inhalativem Kortikosteroid und langwirksamem Beta-2-Agonisten) angezeigt ist: • Patienten, die mit inhalativen Kortikosteroiden und inhalativen schnellwirksamen Beta-2-Agonisten zur bedarfsweisen Inhalation nicht ausreichend eingestellt sind oder • Patienten, die mit inhalativen Kortikosteroiden und langwirksamen Beta-2-Agonisten in Kombination bereits ausreichend eingestellt sind. (FI Foster, Stand 12/2016)
Budesonid/ Formoterol R03AK07 DUORESP Spiromax®	DuoResp® Spiromax® wird nur bei Erwachsenen ab 18 Jahren angewendet. Zur regelmäßigen Behandlung von Asthma, bei der die Anwendung eines inhalativen Kortikosteroids und eines langwirksamen Beta-Agonisten in Kombination angezeigt ist: - bei Patienten, die mit inhalativen Kortikosteroiden und kurzwirksamen Beta-2-Agonisten zur bedarfsweisen Inhalation nicht ausreichend eingestellt sind, oder - bei Patienten, die bereits mit inhalativen Kortikosteroiden und langwirksamen Beta-2-Agonisten in Kombination ausreichend eingestellt sind. (FI DuoResp® Spiromax®, Stand 07/2016)
Salmeterol/ Fluticason R03AK06 Viani®	Viani Diskus ist indiziert für die regelmäßige Behandlung von Asthma bronchiale, bei der die Anwendung von langwirksamem Beta2- Agonisten und inhalativem Kortikoid in Kombination angezeigt ist: – bei Patienten, die mit inhalativen Kortikoiden und kurzwirksamen Beta2-Agonisten zur bedarfsweisen Inhalation nicht ausreichend eingestellt sind oder – bei Patienten, die mit inhalativen Kortikoiden und langwirksamen Beta2-Agonisten ausreichend eingestellt sind. Hinweis: Die Stärke Viani 50 µg/100 µg ist nicht angezeigt bei Erwachsenen und Kindern mit schwerem Asthma bronchiale. (FI Viani®, Stand 04/2015)
Formoterol/ Fluticason	Die Fixkombination aus Fluticason-17-propionat und Formoterolfumarat-Dihydrat wird bei Erwachsenen und Jugendlichen ab 12 Jahren angewendet zur regelmäßigen Behandlung von Asthma bronchiale in Fällen, in denen ein Kombinationspräparat

II. Zugelassene Arzneimittel im Anwendungsgebiet	
R03AK11 FLUTIFORM®	(ein inhalatives Kortikosteroid und ein langwirksamer Beta-2-Agonist) angezeigt ist: - Bei Patienten, die mit inhalativen Kortikosteroiden und bedarfsweise angewendeten, kurzwirksamen inhalativen Beta-2-Agonisten nicht ausreichend eingestellt sind. oder - Bei Patienten, die bereits mit einem inhalativen Kortikosteroid und einem langwirksamen Beta-2-Agonisten adäquat eingestellt sind. (FI flutiform®, Stand 06/2015)
Vilanterol/ Fluticason R03AK10 Relvar® Ellipta®	Relvar Ellipta ist angezeigt für die regelmäßige Behandlung von Asthma bei Erwachsenen und Jugendlichen ab 12 Jahren, bei denen ein Kombinationspräparat (langwirksamer Beta2-Agonist und inhalatives Kortikosteroid) angezeigt ist: • Patienten, die mit inhalativen Kortikosteroiden und einer Bedarfsmedikation mit inhalativen kurzwirksamen Beta2-Agonisten nicht ausreichend eingestellt sind. […] (FI Relvar® Ellipta®, Stand 10/2016)
Kombinationspräparate: Anticholininergika/ Beta-2-Sympathomimetikum	
Ipratropiumbromid/ Fenoterol R03AL01 Berodual N®	Zur Verhütung und Behandlung von Atemnot bei chronisch obstruktiven Atemwegserkrankungen: Asthma bronchiale allergischer und nichtallergischer (endogener) Ursache, Anstrengungsasthma und chronisch obstruktive Bronchitis mit und ohne Emphysem. Hinweis: Sofern eine Dauerbehandlung erforderlich ist, soll stets eine begleitende antiinflammatorische Therapie erfolgen. (FI Berodual®, Stand 10/2014)

Quellen: AMIS-Datenbank, Fachinformationen

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie (zVT):

Inhalt

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und evidenzbasierten systematischen Leitlinien zur Indikation *Asthma* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 31.01.2018 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, Clinical Evidence, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 1211 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 40 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Indikation:

Add-On-Erhaltungstherapie bei erwachsenen Patienten mit schwerem eosinophilem Asthma, das trotz hochdosierter inhalativer Kortikosteroide plus langwirksamer Beta-Agonisten unzureichend kontrolliert ist.

Abkürzungen:

Akdae	Arzneimittelkommission der deutschen Ärzteschaft
ACQ	Asthma Control Questionnaire
AE	adverse events
AQLQ	Asthma Quality of Life Questionnaire
ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BUD	budesonide
CCO	Cancer Care Ontario
DAHTA	DAHTA-Datenbank
F	formoterol
FEV1	forciertes exspiratorisches Volumen (engl. Forced Expiratory Volume in 1 second)
FP	fluticasone
FVC	Forced vital capacity
G-BA	Gemeinsamer Bundesausschuss
GINA	Global Initiative for Asthma
GIN	Guidelines International Network
ICS	inhaled corticosteroids
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
LABA	long-acting beta2-agonists
LAMA	long-acting muscarinic antagonist
NGC	National Guideline Clearinghouse
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence
OCS	orales Glucocorticosteroid
PEF	Peak expiratory flow
SABA	short-acting beta-agonist
SAE	Serious adverse events
SAL	salmeterol
SIGN	Scottish Intercollegiate Guidelines Network
SiT	'single inhaler therapy'
TRIP	Turn Research into Practice Database
WHO	World Health Organization

IQWiG Berichte/G-BA Beschlüsse

G-BA, 2017 [14].	**Anwendungsgebiet (laut Zulassung vom 16. August 2016):**

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Reslizumab Vom 6. Juli 2017 *siehe auch:* **IQWiG, 2017 [21].** **und IQWiG, 2017 [20].**	CINQAERO wird angewendet als Zusatztherapie bei erwachsenen Patienten mit schwerem eosinophilem Asthma, das trotz hochdosierter inhalativer Corticosteroide plus einem anderen Arzneimittel zur Erhaltungstherapie nur unzureichend zu kontrollieren ist (siehe Abschnitt 5.1). **Zweckmäßige Vergleichstherapie:** Die zweckmäßige Vergleichstherapie für die Behandlung (Add-on-Therapie) des schweren eosinophilen Asthmas bei erwachsenen Patienten, welche trotz hoher Dosen an inhalativen Corticosteroiden und einem weiteren Controller unkontrolliert sind, ist: eine patientenindividuelle Therapieeskalation: - der hochdosierten inhalativen Corticosteroide und der langwirksamen Bronchodilatatoren (LABA) mit Tiotropium und ggf. orale Corticosteroide* oder - bei IgE-vermittelter Pathogenese des Asthmas ggf. Omalizumab zusätzlich zu hochdosierten inhalativen Corticosteroiden und langwirksamen Bronchodilatatoren (LABA) und ggf. orale Corticosteroide* oder - ggf. der hochdosierten inhalativen Corticosteroide und der Bronchodilatatoren (LABA) mit oralen Corticosteroiden* *Orale Corticosteroide sollten nur kurzzeitig und in der niedrigst-wirksamen Dosis eingesetzt werden. **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:** a) Patienten mit schwerem eosinophilem Asthma, die nicht oder nur im Rahmen von akuten Exazerbationen mit oralen Corticosteroiden behandelt werden: Ein Zusatznutzen ist nicht belegt. b) Patienten mit schwerem eosinophilem Asthma, die auch über die Behandlung akuter Exazerbationen hinaus regelmäßig mit oralen Corticosteroiden behandelt werden: Anhaltspunkt für einen geringen Zusatznutzen.
G-BA, 2016 [13]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach §	**Zugelassenes Anwendungsgebiet (laut Zulassung vom 2. Dezember 2015):** „Nucala® ist angezeigt als Zusatzbehandlung bei schwerem refraktärem eosinophilem Asthma bei erwachsenen Patienten." **Zweckmäßige Vergleichstherapie:** Die zweckmäßige Vergleichstherapie für Mepolizumab als Zusatztherapie bei erwachsenen Patienten mit schwerem refraktärem eosinophilem Asthma ist: eine patientenindividuelle Therapieeskalation der mittel- bis hochdosierten inhalativen Corticosteroide und der langwirksamen Bronchodilatatoren (LABA) ggf. mit oralen Corticosteroiden (kurzzeitig) in der niedrigst-wirksamen Dosis oder mit Tiotropium oder ggf. bei IgE-vermittelter Pathogenese des Asthmas Omalizumab zusätzlich zu hochdosierten inhalativen Corticosteroiden und langwirksamen Bronchodilatatoren (LABA) und ggf. der oralen Corticosteroidtherapie.

35a SGB V – Mepolizumab Vom 21. Juli 2016 *siehe auch:* **IQWiG, 2016 [18].** **und IQWiG, 2016 [19].**	**Vergleichstherapie:** a) Patienten mit schwerem refraktärem eosinophilem Asthma, die nicht oder nur im Rahmen von akuten Exazerbationen mit oralen Corticosteroiden behandelt werden: Ein Zusatznutzen ist nicht belegt. b) Patienten mit schwerem refraktärem eosinophilem Asthma, die auch über die Behandlung akuter Exazerbationen hinaus regelmäßig mit oralen Corticosteroiden behandelt werden: Anhaltspunkt für einen geringen Zusatznutzen.
G-BA, 2015 [12]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL) in Anlage IV: Therapiehinweis zu Omalizumab	Wirkstoff: Omalizumab (Xolair®) Zugelassene Anwendungsgebiete Omalizumab ist zugelassen als Zusatztherapie zur verbesserten Asthmakontrolle bei: **Erwachsenen und Jugendlichen (ab 12 Jahren)** • mit schwerem persistierendem allergischem Asthma, • die einen positiven Hauttest oder In-vitro-Reaktivität gegen ein ganzjährig auftretendes Aeroallergen zeigen und • sowohl eine reduzierte Lungenfunktion (FEV1 < 80%) haben • als auch unter häufigen Symptomen während des Tages oder nächtlichem Erwachen leiden und • trotz täglicher Therapie mit hochdosierten inhalativen Kortikosteroiden und einem lang wirkenden inhalativen Beta-2-Agonisten mehrfach dokumentierte, schwere Asthma-exazerbationen hatten. • Die Behandlung mit Omalizumab sollte nur bei Patienten in Betracht gezogen werden, bei denen von einem IgE-vermittelten Asthma ausgegangen werden kann. Empfehlungen zur wirtschaftlichen Verordnungsweise: Der Therapiehinweis bezieht sich ausschließlich auf die Indikation Asthma bronchiale. Die Verordnung von Omalizumab ist als Zusatztherapie bei Jugendlichen ab 12 Jahren und Erwachsenen nur wirtschaftlich, die kumulativ folgende Voraussetzungen erfüllen: - schweres persistierendes allergisches Asthma, - reduzierte Lungenfunktion (FEV1 < 80%), - positiver Hauttest oder In-vitro-Reaktivität gegen ein ganzjährig auftretendes und vom Patienten nicht vermeidbares Aeroallergen, - das Asthma ist IgE-vermittelt mit IgE-Werten zwischen ≥ 76 und ≤ 1500 I.E./ml vor Beginn der Behandlung, - häufige dokumentierte Symptome während des Tages oder nächtliches Erwachen, - trotz täglicher Therapie mit hochdosierten inhalativen Kortikosteroiden (entsprechend > 1000 µg pro Tag Beclometason oder Äquivalent) und mindestens einem lang wirkenden inhalativen Beta-2-Agonisten als Kontroller traten

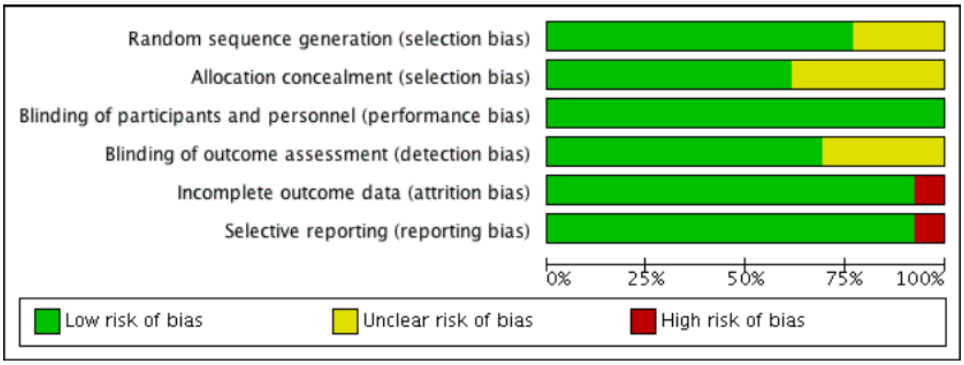
	- in den letzten 12 Monaten mindestens zwei unabhängige, dokumentierte schwere Asthmaexazerbationen, die mit systemischen Kortikosteroiden behandelt wurden, oder - eine Exazerbation, die systemische Kortikosteroidgabe notwendig machte und zur Krankenhausaufnahme bzw. Notfallbehandlung führte, auf. - das Körpergewicht liegt innerhalb der Grenzen der Dosierungstabelle also ≥ 20 kg und ≤ 150 kg. - Nichtraucher
G-BA, 2017 [15]. Richtlinie des Gemeinsamen Bundesausschusses zur Regelung von Anforderungen an die Ausgestaltung von Strukturierten Behandlungsprogrammen nach §137f Abs. 2 SGB V (DMP-Richtlinie/DMP-RL) in Kraft getreten am: 1. Oktober 2017	**Fazit:** **1.5.6 Medikamentöse Maßnahmen** Zur medikamentösen Therapie sind mit der Patientin oder dem Patienten ein individueller Therapieplan zu erstellen und Maßnahmen zum Selbstmanagement zu erarbeiten (siehe auch strukturierte Schulungsprogramme (Ziffer II 4)). Vorrangig sollen unter Berücksichtigung der Kontraindikationen und der Patientenpräferenzen Medikamente verwendet werden, deren positiver Effekt und Sicherheit im Hinblick auf die unter Ziffer II 1.3 genannten Therapieziele in prospektiven, randomisierten, kontrollierten Studien Nachgewiesen wurde. Dabei sollen diejenigen Wirkstoffe/Wirkstoffgruppen Kombinationen bevorzugt werden, die diesbezüglich den größten Nutzen erbringen. Sofern im Rahmen der oder individuellen Therapieplanung andere Wirkstoffgruppen oder Wirkstoffe als die in dieser Anlage genannten verordnet werden sollen, ist die Patientin oder der Patient darüber zu informieren, ob für diese Wirksamkeitsbelege bezüglich der unter Ziffer II 1.3 genannten Therapieziele vorliegen. In der medikamentösen Behandlung des Asthma bronchiale werden Dauertherapeutika (Medikamente, die regelmäßig eingenommen werden) und Bedarfstherapeutika (Medikamente, die bei Bedarf, z. B. bei zu erwartenden körperlichen Belastungssituationen, zur Behandlung von Dyspnoe und insbesondere bei Asthma-Anfällen eingesetzt werden) unterschieden. In der Inhalationstherapie ist nur die im Bronchialsystem deponierte Medikamentenmenge wirksam. Diese hängt stark ab von der individuellen Anatomie der Atemwege, dem Atemmuster, der Partikelgröße und dem Inhalationssystem. Es sollte daher das Inhalationssystem und die Instruktion bezüglich der Anwendung individuell an die Bedürfnisse und Fähigkeiten (insbesondere Alter und Koordination) angepasst werden. Darüber hinaus ist es sinnvoll, bei Verwendung mehrerer inhalativer Medikamente für alle Präparate den gleichen Typ von Inhalationssystem einzusetzen. 0Nach einer initialen Einweisung in die Inhalationstechnik sollte diese in jedem Dokumentationszeitraum mindestens einmal überprüft werden. Bei guter Asthma-Kontrolle über einen längeren Zeitraum (z. B. über drei Monate bei Einsatz inhalativer Glukokortikosteroide) soll die

	Reduktion der Therapie erwogen werden. **1.5.6.1 Dauertherapie bei Erwachsenen** Vorrangig sollen zur Dauertherapie die folgenden Wirkstoffgruppen verwendet werden: 1. Basistherapie - inhalative Glukokortikosteroide, 2. als Erweiterung dieser Basistherapie kommen in Betracht: - inhalative lang wirksame Beta-2-Sympathomimetika - in begründeten Fällen - systemische Glukokortikosteroide - Leukotrien-Rezeptor-Antagonisten - Theophyllin (Darreichungsform mit verzögerter Wirkstofffreisetzung) - Anti-IgE Antikörper Bei Patientinnen und Patienten mit, trotz Ausschöpfung einer erweiterten Basistherapie nicht ausreichend kontrollierbarem, schwerem persistierendem allergischem Asthma bronchiale kann eine Behandlung mit Anti-IgE Antikörper geprüft werden. Bei Undurchführbarkeit einer Therapie mit inhalativen Glukokortikosteroiden (z. B. Ablehnung oder Unverträglichkeit) als Basismedikation ist vor Verordnung einer unterlegenen, alternativen antientzündlichen Therapie ein Aufklärungsgespräch über Risiken dieser Therapieoptionen zu führen. **1.5.6.2 Dauertherapie bei 5-17 Jährigen** Vorrangig sollen zur Dauertherapie die folgenden Wirkstoffgruppen verwendet werden: 1. Basistherapie - Vorzugsweise inhalative Glukokortikosteroide - in begründeten Fällen alternativ Leukotrien-Rezeptor-Antagonisten 2. als Erweiterung dieser Basistherapie kommen in Betracht: - Steigerung der Dosis des inhalativen Glukokortikosteroids auf eine mittelhohe Dosis - Kombination von inhalativen Glukokortikosteroiden und Leukotrien-Rezeptor-Antagonisten - inhalative lang wirksame Beta-2-Sympathomimetika (nur in Kombination mit inhalativen Glukokortikosteroiden 3. Im Ausnahmefall, bei sonst nichtkontrollierbaren Verläufen - systemische Glukokortikosteroide - Theophyllin (Darreichungsform mit verzögerter Wirkstofffreisetzung) - Anti-IgE Antikörper Bei Patientinnen und Patienten mit, trotz Ausschöpfung einer erweiterten Basistherapie nicht ausreichend kontrollierbarem,

	schwerem persistierendem allergischem Asthma bronchiale kann eine Behandlung mit Anti-IgE Antikörper geprüft werden. Die Verordnung von Medikamenten nach 3. sollte durch die jeweils qualifizierte Fachärztin/den jeweils qualifizierten Facharzt oder durch die qualifizierte Einrichtung erfolgen. **1.5.6.3 Bedarfstherapie/Anfallstherapie** Eine Bedarfsmedikation kann beispielsweise bei körperlicher Belastung, Dyspnoe, pulmonalen Infekten oder Obstruktionen unterschiedlichen Schweregrades notwendig sein. Vorrangig sollten bei der Bedarfstherapie/Anfallstherapie folgende Wirkstoffgruppen Anwendung finden: - rasch wirksame Beta-2-Sympathomimetika (bevorzugt inhalativ), - kurz wirksame Anticholinergika (5-17 Jährige) Bei unzureichendem Ansprechen kommen in Betracht: - systemische Glukokortikosteroide (maximal bis zu 2 Wochen), - kurz wirksame Anticholinergika - Theophyllin (Darreichungsform mit rascher Wirkstofffreisetzung). Der Asthma-Anfall kann durch Infekte, Allergenexposition, Medikamentenunverträglichkeit, irritativ-toxische Ursachen sowie körperliche Belastung hervorgerufen werden. Die Gabe von Antibiotika ist im Asthma-Anfall in der Regel nicht indiziert.
G-BA, 2017 [16]. Richtlinie des Gemeinsamen Bundesausschusses zur Zusammenführung der Anforderungen an strukturierte Behandlungsprogramme nach § 137f Abs. 2 SGB V (DMP-Anforderungen-Richtlinie/DMP-A-RL) Inkrafttreten: 18. November 2017	**Anlage 9** **Anforderungen an strukturierte Behandlungsprogramme für Patientinnen und Patienten mit chronisch obstruktiven Atemwegserkrankungen - Teil 1 Asthma bronchiale** [1]Die Regelungen des Teil B II. Ziffer 1-4 der DMP-Richtlinie gelten bis zum Inkrafttreten der Anforderungen an die Ausgestaltung des strukturierten Behandlungsprogramms Für Patientinnen und Patienten mit chronischen obstruktiven Atemwegserkrankungen – Asthma bronchiale – in dieser Richtlinie. [2]Die medizinischen Evaluationsparameter für das strukturierte Behandlungsprogramm Asthma bronchiale werden zukünftig in der Ziffer 5 dieser Anlage normiert. **Anlage 10 Asthma bronchiale - Dokumentation** Die Regelungen des Teil B II. Ziffer 5 der DMP-Richtlinie gelten bis zum Inkrafttreten der Regelungen zur Dokumentation des strukturierten Behandlungsprogramms chronisch obstruktive Atemwegserkrankungen – Asthma bronchiale – in dieser Richtlinie.

Cochrane Reviews

Farne HA et al., 2017 [11]. Anti-IL5 therapies for asthma	1. Fragestellung We considered in this review whether taking the new drugs mepolizumab, reslizumab or benralizumab in addition to standard treatment (e.g. inhaled steroids and combination inhalers) are better than a placebo for people with asthma.
	2. Methodik Population: adults and children with a diagnosis of asthma. We focused on collating data from people who had been reported as having eosinophilic asthma to analyse these individuals as a subgroup. Intervention: anti-IL-5 therapy Komparator: placebo Endpunkt: primary: 'Clinically significant' asthma exacerbation, as defined by treatment with a course (three days or more) of systemic corticosteroids (with or without hospital admission); secondary: 1. Asthma exacerbation requiring hospital admission, 2. HRQoL (as measured by a validated questionnaire e.g. ACQ, AQLQ, SGRQ), 3. Measures of lung function (e.g. FEV1), 4. Serious adverse events, 5. 'Clinically significant' adverse events, as defined by those that prompted discontinuation of the intervention and withdrawal from the study, 6. Eosinophil counts in peripheral blood Reporting one ormore of the outcomes listed here in the trial was not an inclusion criterion for the review. Recherche: The search was first conducted in 11/2013 and was updated in 11/2014 and 03/2017. Anzahl eingeschlossene Studien/Patienten (Gesamt): 13 studies included in the qualitative synthesis; 12 studies included in the quantitative synthesis Qualitätsbewertung der Studien: risk of bias for each study using the criteria outlined intheCochraneHandbook for Systematic Reviews of Interventions
	3. Ergebnisse: Qualität der Studien: The evidence included in this review is provided by very well-designed studies. We consider these studies to be at low risk of bias in the following important respects: the procedure that determined who received which treatment, the blinding processes and the clarity of detail concerning participants who did not complete the study. Overall the evidence was high to moderate quality.



- four included studies comparing mepolizumab versus placebo
- four included studies comparing reslizumab versus placebo

Mepolizumab (SC) compared to placebo for asthma

Patient or population: people with asthma
Setting: community
Intervention: mepolizumab (SC)
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with mepolizumab (SC)				
Rate of exacerbations requiring systemic corticosteroids Follow-up: range 24 to 32 weeks	The mean rate in the placebo group was 1.48 events per participant per year[a]	The mean rate in the intervention group was 0.81 fewer events per participant per year (95% CI 0.66 fewer to 0.94 fewer)	Rate ratio 0.45 (0.36 to 0.55)	936 (2 RCTs)	⊕⊕⊕⊕ High	
Rate of exacerbations requiring emergency department treatment or admission Follow-up: range 24 to 32 weeks	The mean rate in the placebo group was 0.15 events per patient per year[b]	The mean rate in the intervention group was 0.10 fewer events per participant per year (95% CI 0.05 fewer to 0.12 fewer)	Rate ratio 0.36 (0.20 to 0.66)	936 (2 RCTs)	⊕⊕⊕⊕ High	
Health-related quality of life (ACQ) Scale from: 0 to 6 (lower is better) Follow-up: range 24 to 32 weeks	The mean change in the placebo group ranged from −0.4 to −0.5 units	The mean in the intervention group was -0.42 units fewer (-0.56 fewer to -0.28 fewer)	-	936 (2 RCTs)	⊕⊕⊕◯ Moderate[c]	A change of ≥ 0.5 is considered the minimum clinically significant difference
Health-related quality of life (SGRQ) Scale from: 0 to 100 (lower is better) Follow-up: range 24 to 32 weeks	The mean change in the placebo group ranged from −7.9 to −9.0 units	The mean change in the intervention group was -7.4 units fewer (-9.5 fewer to -5.29 fewer)	-	936 (2 RCTs)	⊕⊕⊕⊕ High	A change of ≥ 4 is considered the minimum clinically significant difference
Pre-bronchodilator FEV_1 (L) Follow-up: range 24 to 32 weeks	The mean change in the placebo group ranged from 0.086 L (± 0.031 L) to 0.120 L (0.047 to 0.192 L)	The mean difference from placebo was a further 0.11 L (0.06 L to 0.17 L)	-	936 (2 RCTs)	⊕⊕⊕⊕ High	
Adverse events leading to discontinuation Follow-up: range 24 to 32 weeks	15 per 1000	7 per 1000 (2 to 27)	Risk ratio 0.45 (0.11 to 1.80)	936 (2 RCTs)	⊕⊕⊕◯ Moderate[d]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

ACQ: Asthma Control Questionnaire; **CI:** confidence interval; **FEV_1** : forced expiratory volume in 1 second; **RR:** risk ratio; **SC**: subcutaneous; **SGRQ**: St. George's Respiratory Questionnaire

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a] Rounded mean of the rate in the placebo group of the two studies: 1.21 and 1.74.
[b] Rounded mean of the rate in the placebo group of the two studies: 0.10 and 0.20.
[c] The mean difference (-0.42) is smaller than the minimum clinically significant difference (a reduction of 0.5 points).
[d] The 95% CI crosses the line of no effect, thus we downgraded the quality of evidence to moderate because of imprecision.

Reslizumab (IV) compared to placebo for asthma

Patient or population: people with asthma
Setting: community
Intervention: reslizumab (IV)
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with reslizumab (IV)				
Rate of exacerbations requiring systemic corticosteroids Follow-up: 52 weeks	The mean rate in the placebo group was 1.54 events per participant per year	The mean rate in the intervention groups was 0.93 fewer events per participant per year (1.09 fewer to 0.73 fewer)	Rate ratio 0.43 (0.33 to 0.55)	953 (2 RCTs)	⊕⊕⊕⊕ High	
Rate of exacerbations requiring emergency department treatment or admission Follow-up: 52 weeks	The mean rate in the placebo group was 0.12 events per participant per year	The mean rate in the intervention groups was 0.04 fewer events per participant per year (0.07 fewer to 0.02 more)	Rate ratio 0.67 (0.39 to 1.17)	953 (2 RCTs)	⊕⊕⊕⊕ High	
Health-related quality of life (AQLQ) Scale from: 1 to 7 (higher is better) Follow -p: range 16 weeks to 52 weeks	The mean change in the placebo group ranged from 0.779 to 0.89 units	MD 0.28 higher (0.17 higher to 0.39 higher)[a]	-	1164 (3 RCTs)	⊕⊕⊕⊕ High	A change of ≥ 0.5 is considered the minimum clinically significant difference
Health-related quality of life (ACQ) Scale from: 0 to 6 (lower is better) Follow-up: range 16 weeks to 52 weeks	The mean change in the placebo group ranged from −0.368 to −0.80 units	MD -0.25 lower (-0.33 lower to -0.17 lower)[b]	-	1652 (4 RCTs)	⊕⊕⊕⊕ High	A change of ≥ 0.5 is considered the minimum clinically significant difference
Pre-bronchodilator FEV_1 (L) Follow-up: range 16 weeks to 52 weeks	The mean change in the placebo group ranged from 0.002 L (± 0.1216 L) to 0.215 (± 0.0484 L)	MD 0.11 L higher (0.07 L higher to 0.15 L higher)	-	1652 (4 RCTs)	⊕⊕⊕⊕ High	
Serious adverse events Follow-up: range 16 weeks to 52 weeks	91 per 1000	72 per 1000 (51 to 102)	RR 0.79 (0.56 to 1.12)	1656 (4 RCTs)	⊕⊕⊕⊕ High	
Adverse events leading to discontinuation Follow-up: range 16 weeks to 52 weeks	58 per 1000	38 per 1000 (25 to 59)	RR 0.66 (0.43 to 1.02)	1659 (4 RCTs)	⊕⊕⊕⊕ High	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

ACQ: Asthma Control Questionnaire; **AQLQ**: Asthma Quality of Life Questionnaire; **CI:** confidence interval; **FEV_1** : forced expiratory volume in 1 second; **MD**: mean difference; **IV**: intravenous; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a] The mean difference (0.28) is smaller than the minimum clinically significant difference (a reduction of 0.5 points).
[b] The mean difference (-0.25) is smaller than the minimum clinically significant difference (a reduction of 0.5 points)

4. Anmerkungen/Fazit der Autoren

   We found that participants with severe asthma, who had high numbers of a certain type of inflammatory cell (eosinophils) in the blood, benefited from taking mepolizumab, reslizumab or benralizumab through reduced asthma attacks. There were small improvements in quality of life and breathing tests, but these may be too small to be detected by patients. We agree with international guidelines that say that these treatments can be added to standard treatment for people with severe asthma. However, we think that further research is needed to clarify some aspects, such as how to assess treatment response and how long to give treatment for.

5. *Kommentare zum Review*

- Studien zum Wirkstoff Benralizumab aufgrund fehlender Zulassung im AWG nicht dargestellt

Kew KM et al., 2016 [22]. Long-acting muscarinic antagonists (LAMA) added to combination long-acting beta2-agonists and inhaled corticosteroids (LABA/ICS) versus LABA/ICS for adults with asthma (Review)	1. Fragestellung To assess the effects of adding a long-acting muscarinic antagonist (LAMA) to combination long-acting beta2-agonists (LABA) and inhaled corticosteroids (ICS) in adults whose asthma is not well controlled by LABA/ICS.
	2. Methodik Population: studies in adults (aged 18 years or older) with asthma who were taking LABA/ICS combination therapy Intervention/ Komparator: (1) LAMA add-on to any dose of LABA/ ICS combination therapy versus the same dose of LABA/ICS alone (2) LAMA versus placebo (if they required participants to be taking LABA/ICS combination therapy for inclusion in the trial) (3) We included studies involving the addition of the following LAMA at any dose. • Tiotropium (Spiriva Handihaler or Respimat). • Aclidinium bromide (Eklira Genuair). • Glycopyrronium bromide (Seebri Breezhaler). (4) allowed participants to continue using additional short- or long-acting medications (e.g. salbutamol, terbutaline and ipratropium, leukotriene receptor antagonists), provided they were not part of the randomised treatment. Endpunkte: (1) primäre Endpunkte: Exacerbations requiring oral corticosteroids; Quality of life (measured on a validated asthma scale, e.g. Asthma Quality of Life Questionnaire, AQLQ); Serious adverse events (all causes) (2) sekundäre Endpunkte: Exacerbations requiring hospital admission; Lung function (preferably trough forced expiratory volume in one second, or FEV1); Asthma control (measured on a validated scale, e.g. Asthma Control Questionnaire (ACQ), Asthma Control Test); Any adverse events Suchzeitraum (Aktualität der Recherche): bis Januar 2016 Anzahl eingeschlossene Studien/Patienten (Gesamt): 4 RCTs (n=1197) Qualitätsbewertung der Studien: Cochrane Risk of Bias Tool; geplante Sensitivitätsanalyse für die primären Endpunkte unter Ausschluss von Studien mit hohem Verzerrungspotential, nicht-publizierten Daten und Cross-over-Studien Heterogenität: I^2 nach Higgins/Thompson
	3. Ergebnisdarstellung

- 4 double-blind, double-dummy trials comparing LAMA to placebo, including 1197 people with asthma taking combination LABA/ICS → für die quanititative Analyse wurden 3 Studien eingeschlossen

Qualitätsbewertung: low risk of bias across domains

Ergebnisse: LAMA + LABA/ICS vs LABA/ICS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Exacerbations requiring oral corticosteroids (patients with at least one)	2	907	Odds Ratio (M-H, Random, 95% CI)	0.76 [0.57, 1.02]
2 Exacerbations requiring oral corticosteroids (number per patient)	2	907	Rate Ratio (Random, 95% CI)	0.79 [0.53, 1.17]
3 Time to first exacerbation requiring oral corticosteroids	2	907	Hazard Ratio (Random, 95% CI)	0.80 [0.63, 1.01]
4 Quality of life (AQLQ)	2	907	Mean Difference (IV, Random, 95% CI)	0.09 [-0.03, 0.20]
5 Serious adverse events	3	1197	Odds Ratio (M-H, Random, 95% CI)	0.60 [0.24, 1.47]
6 Exacerbations requiring hospital admission	3	1191	Risk Difference (M-H, Random, 95% CI)	-0.01 [-0.04, 0.01]
7 Lung function (change in trough FEV_1 L)	3	1191	Mean Difference (IV, Random, 95% CI)	0.07 [0.03, 0.11]
8 Lung function (change in trough FVC)	3	1191	Mean Difference (IV, Random, 95% CI)	0.07 [0.02, 0.13]
9 Asthma control (ACQ)	2	907	Mean Difference (IV, Random, 95% CI)	-0.13 [-0.23, -0.02]
10 Asthma control (ACQ responder)	2	1192	Odds Ratio (M-H, Random, 95% CI)	1.42 [0.88, 2.29]
11 Any adverse events	3	1197	Odds Ratio (M-H, Random, 95% CI)	0.70 [0.52, 0.94]
12 Quality of life (AQLQ) by timeframe	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
12.1 24-26 weeks	2	907	Mean Difference (IV, Random, 95% CI)	0.11 [-0.03, 0.24]
12.2 48-52 weeks	2	907	Mean Difference (IV, Random, 95% CI)	0.09 [-0.03, 0.20]

- People randomised to take a LAMA add-on had fewer exacerbations requiring oral corticosteroids than those continuing to take LABA/ICS alone, although the confidence intervals included no difference (OR 0.76, 95% CI 0.57 to 1.02) = moderate quality
- Over 48 weeks, 328 out of 1000 people taking their usual LABA/ICS would have to take oral corticosteroids for an exacerbation compared with 271 if they took a LAMA as well (95%CI 218 to 333 per 1000).
- Quality of life (AQLQ) was no better for those taking LAMA add-on than those taking LABA/ICS alone when considered in light of the 0.5 minimal clinically important difference on the scale (MD 0.09, 95% CI − 0.03 to 0.20)
- evidence for whether LAMA increased or decreased serious adverse events in this population was inconsistent (OR 0.60, 95% CI 0.24 to 1.47; I2 = 76%).

high quality evidence showing benefits to lung function (trough FEV1 and FVC) and potentially small benefits to asthma control. People taking a LAMA add-on were less likely to experience non-serious adverse events.

4. Anmerkungen/Fazit der Autoren: Tiotropium add-on may have additional benefits over LABA/ICS alone to reduce the need for rescue oral steroids in people with severe asthma. The effect was imprecise, and there was no evidence for other LAMA preparations. Possible benefits on quality of life were negligible, and evidence for the effect on serious adverse events was inconsistent. There are likely to be small

	added benefits of tiotropium Respimat 5 µg daily on lung function and asthma control over LABA/ICS alone, and fewer non-serious adverse events. The benefit of tiotropium add-on on the frequency of hospital admission is not yet known, despite year-long trials. 5. Hinweise durch FB Med • The studies added tiotropium Respimat to LABA/ICS therapy; however the exact LABA/ICS combination was not specified all of the studies were funded by industry
Kew KM et al., 2015 [23]. Long-acting muscarinic antagonists (LAMA) added to inhaled corticosteroids (ICS) versus addition of long-acting beta2- agonists (LABA) for adults with asthma (Review)	1. Fragestellung To assess the efficacy and safety of adding a LAMA to ICS compared with adding a LABA for adults whose asthma is not well controlled on ICS alone.
	2. Methodik <u>Population:</u> adults (aged 18 years or older) whose asthma is not well controlled with ICS alone <u>Intervention:</u> LAMA add-on <u>Komparator:</u> LABA add-on → Studies involving the addition of the following LAMAs at any dose: • tiotropium (Spiriva HandiHaler or Respimat); • aclidinium bromide (Eklira Genuair); • glycopyrronium bromide (Seebri Breezhaler). → Eligible comparison groups were randomised to receive the same dose of ICS as the intervention group, with the addition of any of the following LABAs: • formoterol 12 or 24 mcg twice daily • salmeterol 50 mcg twice daily • vilanterol 22 mcg once daily <u>Endpunkte:</u> (1) primäre Endpunkte: Exacerbations requiring oral corticosteroids; Quality of life (measured on a validated asthma scale, e.g. Asthma Quality of Life Questionnaire, AQLQ); Any serious adverse event. (2) sekundäre Endpunkte: Exacerbations requiring hospital admission; Lung function (in particular, trough forced expiratory volume in one second (FEV1)); Asthma control (measured on a validated scale, e.g. Asthma Control Questionnaire (ACQ), Asthma Control Test); Any adverse events <u>Suchzeitraum (Aktualität der Recherche):</u> bis April 2015 <u>Anzahl eingeschlossene Studien/Patienten (Gesamt):</u> 4 RCTs (n= 2049) <u>Qualitätsbewertung der Studien:</u> Cochrane Risk of Bias Tool; geplante

Sensitivitätsanalyse für die primären Endpunkte unter Ausschluss von Studien mit hohem Verzerrungspotential, nicht-publizierten Daten

Heterogenität: I^2 nach Higgins/Thompson (greater than 30% → they reported it and explored possible causes by pre-specified subgroup analysis)

→ a priori definierte Subgruppen:

- Duration of therapy (six months or less, more than six months).
- Corticosteroid dose (according to GINA 2014 – defined low, medium and high cut-offs).
- Dose and type of LABA (e.g. formoterol 24 mcg, salmeterol 50 mcg).

Dose and type of LAMA (e.g. tiotropium HandiHaler 18 mcg, tiotropium Respimat 5 mcg).

3. Ergebnisdarstellung

- 4 Studien eingeschlossen

Qualitätsbewertung: several studies were given high risk of bias ratings, particularly in the blinding domains and selective reporting, and there was some uncertainty in others, mostly due to insufficient reporting. However, most of the high risk of bias judgements were associated with studies that did not contribute data to the metaanalyses.

Ergebnisse:

Comparison 1. Long-acting muscarinic antagonists (LAMA) add-on versus long-acting beta$_2$-agonists (LABA) add-on

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Exacerbations (oral corticosteroid)	2		Odds Ratio (Random, 95% CI)	1.05 [0.50, 2.18]
2 Asthma Quality of Life Questionnaire (AQLQ) total	4		Mean Difference (Random, 95% CI)	-0.12 [-0.18, -0.05]
3 Serious adverse events (all)	4		Odds Ratio (Random, 95% CI)	0.84 [0.41, 1.73]
4 Exacerbations (hospital)	4		Odds Ratio (Random, 95% CI)	0.72 [0.18, 2.92]
5 Trough forced expiratory volume in 1 second (FEV_1) (L)	4		Mean Difference (Random, 95% CI)	0.05 [0.01, 0.09]
6 Peak FEV_1 (L)	3		Mean Difference (Random, 95% CI)	Totals not selected
7 Trough peak expiratory flow (PEF) (L/min)	4		Mean Difference (Random, 95% CI)	5.78 [0.86, 10.71]
8 Trough forced vital capacity (FVC) (L)	3	1745	Mean Difference (IV, Random, 95% CI)	0.03 [-0.02, 0.07]
9 Peak FVC (L)	2	1483	Mean Difference (IV, Random, 95% CI)	-0.00 [-0.04, 0.03]
10 Asthma Control Questionnaire (ACQ) total	3		Mean Difference (Random, 95% CI)	0.06 [0.00, 0.13]
11 ACQ response	2	1563	Odds Ratio (M-H, Random, 95% CI)	0.91 [0.73, 1.13]
12 Adverse events AEs (all)	3	1839	Odds Ratio (IV, Random, 95% CI)	1.11 [0.92, 1.35]
13 AEs classified as asthma	3	1839	Odds Ratio (M-H, Random, 95% CI)	0.95 [0.74, 1.22]

Comparison 3. Long-acting muscarinic antagonists (LAMA) dose head-to-head

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Exacerbations (oral corticosteroid)	1	1036	Odds Ratio (M-H, Fixed, 95% CI)	0.69 [0.40, 1.22]
2 Asthma Quality of Life Questionnaire (AQLQ) total	2	973	Mean Difference (IV, Random, 95% CI)	0.01 [-0.09, 0.10]
3 Serious adverse events (SAEs) (all)	2	1036	Odds Ratio (M-H, Random, 95% CI)	1.09 [0.47, 2.49]

Comparison 4. Sensitivity analysis excluding the cross-over trial

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Exacerbations (oral corticosteroid)	1		Odds Ratio (IV, Random, 95% CI)	Totals not selected
2 Asthma Quality of Life Questionnaire (AQLQ) total	3	1745	Mean Difference (IV, Random, 95% CI)	-0.11 [-0.19, -0.03]
3 Serious adverse events (SAEs) (all)	3	1839	Odds Ratio (IV, Random, 95% CI)	0.79 [0.30, 2.07]

- Studies reporting exacerbations requiring OCS showed no difference between the two add-ons, but our confidence in the effect was low due to inconsistency between studies and because the confidence intervals (CI) included significant benefit of either treatment (odds ratio (OR) 1.05, 95%CI 0.50 to 2.18; 1753 participants; 3 studies);
- People taking LAMA scored slightly worse on two scales measuring quality of life (Asthma Quality of Life Questionnaire; AQLQ) and asthma control (Asthma Control Questionnaire; ACQ); the evidence was rated high quality but the effects were small and unlikely to be clinically significant (AQLQ: mean difference (MD) -0.12, 95% CI -0.18 to -0.05; 1745 participants; 1745; 4 studies; ACQ: MD 0.06, 95% CI 0.00 to 0.13; 1483 participants; 3 studies).
- some evidence support small benefits of LAMA over LABA on lung function, including on our pre-specified preferred measure trough forced expiratory volume in one second (FEV1) (MD 0.05 L, 95% CI 0.01 to 0.09; 1745 participants, 4 studies). However, the effects on other measures varied, and it is not clear whether the magnitude of the differences were clinically significant.

  More people had adverse events on LAMA but the difference with LABA was not statistically significant.

4. Anmerkungen/Fazit der Autoren: Direct evidence of long-acting muscarinic antagonists (LAMA) versus long-acting beta2-agonists (LABA) as add-on therapy is currently limited to studies of less than six months comparing tiotropium Respimat to salmeterol, and we do not know how they compare in terms of exacerbations and serious adverse events.

   There is moderate quality evidence that LAMAs show small benefits over LABA on some measures of lung function, and high quality evidence that LABAs are slightly better for quality of life, but the differences were all small. Given the much larger evidence base for

	LABA versus placebo for people whose asthma is not well controlled on ICS, the current evidence is not strong enough to say that LAMA can be substituted for LABA as add-on therapy. 5. Hinweise durch FB Med If studies included adults and adolescents or children under 12 and data were not reported separately, we included them if the mean age in both groups was over 18 years.
Ahmad S et al., 2015 [1]. Stopping long-acting beta2-agonists (LABA) for adults with asthma well controlled by LABA and inhaled corticosteroids.	1. Fragestellung To compare cessation of long-acting beta2-agonists (LABA) versus continued use of LABA/inhaled corticosteroids (LABA/ICS) for adults whose asthma is well controlled, and to determine whether stopping LABA: I. results in loss of asthma control or deterioration in quality of life; II. increases the likelihood of asthma attacks or 'exacerbations'; or III. increases or decreases the likelihood of serious adverse events of any cause.
	2. Methodik <u>Population:</u> adults age 18 or older whose asthma is currently well controlled with any dose of maintenance long-acting beta2-agonists (LABA) and inhaled corticosteroids (ICS). <u>Intervention:</u> LABA stopped <u>Komparator:</u> LABA continued <u>Endpunkte:</u> (1) primäre Endpunkte: Exacerbations requiring oral corticosteroids; Quality of life (measured on a validated asthma scale, e.g. Asthma Quality of Life Questionnaire, AQLQ); Any serious adverse event. (2) sekundäre Endpunkte: Exacerbations requiring hospital admission; Lung function (in particular, trough forced expiratory volume in one second (FEV1)); Asthma control (measured on a validated scale, e.g. Asthma Control Questionnaire (ACQ), Asthma Control Test); Any adverse events; Withdrawals <u>Suchzeitraum (Aktualität der Recherche):</u> bis April 2015 <u>Anzahl eingeschlossene Studien/Patienten (Gesamt):</u> 6 RCTs –Y davon 5 für Metaanalyse relevant (n=2781) <u>Qualitätsbewertung der Studien:</u> Cochrane Risk of Bias Tool; geplante Sensitivitätsanalyse für die primären Endpunkte unter Ausschluss von Studien mit hohem Verzerrungspotential und nicht-publizierten Daten <u>Heterogenität:</u> I^2 nach Higgins/Thompson → a priori definierte Subgruppen:

	• Mean steroid dose (according to GINA 2014, defined as low, medium and high cutoffs). • Type of inhaler used in the comparison group (LABA/ICS combination inhaler vs separate inhalers). Type of LABA being stopped (formoterol, salmeterol).
	3. Ergebnisdarstellung <u>Qualitätsbewertung</u>: Most ratings in most domains for included studies were low risk, with the exception of attrition bias and other bias. <u>Ergebnisse:</u> • Stopping LABA might increase the number of people having exacerbations and requiring oral corticosteroids (odds ratio (OR) 1.74, 95% confidence interval (CI) 0.83 to 3.65; participants = 1257; studies = 4), although the confidence intervals did not exclude the possibility that stopping LABA was beneficial; over 17 weeks, 19 people per 1000 who continued their LABA had an exacerbation, compared with 32 per 1000 when LABA were stopped (13 more per 1000, 95% CI 3 fewer to 46 more). • People who stopped LABA had worse scores on the Asthma Control Questionnaire (mean difference (MD) 0.24, 95% CI 0.13 to 0.35; participants = 645; studies = 3) and on measures of asthma-related quality of life (standardised mean difference (SMD) 0.36, 95% CI 0.15 to 0.57; participants = 359; studies = 2) than those who continued LABA, but the effects were not clinically relevant. • Too few events occurred for investigators to tell whether stopping LABA has a greater effect on serious adverse events compared with continuing LABA+ICS (OR 0.82, 95%CI 0.28 to 2.42; participants = 1342; studies = 5), and no study reported exacerbations requiring an emergency department visit or hospitalisation as a separate outcome. • Stopping LABA may result in fewer adverse events of any kind compared with continuing, although the effect was not statistically significant (OR 0.83, 95% CI 0.66 to 1.05; participants = 1339; studies = 5), stopping LABA made people more likely to withdraw from participation in research studies (OR 1.95, 95% CI 1.47 to 2.58; participants = 1352; studies = 5).
	4. Anmerkungen/Fazit der Autoren This review suggests that stopping LABA in adults who have stable asthma while they are taking a combination of LABA and ICS inhalers may increase the likelihood of asthma exacerbations that require treatment with oral corticosteroids, but this is not certain. Stopping LABA may slightly reduce asthma control and quality of life, but evidence was insufficient to show whether this had an effect on important outcomes such as serious adverse events and exacerbations requiring hospital admission, and longer trials are warranted.

Anderson DE et al., 2015 [2]. Long-acting muscarinic antagonists (LAMA) added to inhaled corticosteroids (ICS) versus the same dose of ICS alone for adults with asthma (Review)	1. Fragestellung To assess the efficacy and safety of a long-acting muscarinic antagonist (LAMA) added to any dose of an inhaled corticosteroid (ICS) compared with the same dose of ICS alone for adults whose asthma is not well controlled.
	2. Methodik Population: adults (aged 18 years or older) whose asthma was not well controlled by ICS alone Intervention: LAMA add-on Komparator: ICS alone Endpunkte: (1) primäre Endpunkte: Exacerbations requiring oral corticosteroids; Quality of life (measured on a validated asthma scale, e.g. Asthma Quality of Life Questionnaire, AQLQ); All-cause serious adverse events (2) sekundäre Endpunkte: Exacerbations requiring hospital admission; Lung function (in particular, trough forced expiratory volume in one second (FEV1)); Asthma control (measured on a validated scale, e.g. Asthma Control Questionnaire (ACQ), Asthma Control Test); Any adverse events Suchzeitraum (Aktualität der Recherche): bis 2015 Anzahl eingeschlossene Studien/Patienten (Gesamt): 5 RCTs (n=2563) Qualitätsbewertung der Studien: Cochrane Risk of Bias Tool; geplante Sensitivitätsanalyse für die primären Endpunkte unter Ausschluss von Studien mit hohem Verzerrungspotential und nicht-publizierten Daten Heterogenität: I^2 nach Higgins/Thompson (greater than 30% → they reported it and explored possible causes by pre-specified subgroup analysis) → unplanned sensitivity analysis on primary outcomes by removing one study in which around half of the participants were taking a LABA, which was outside the inclusion criteria. → a priori definierte Subgruppen: • Duration of therapy (≤ 6 months, > 6 months). • Corticosteroid dose (according to GINA 2014, defined as low, medium and high cutoffs). Dose and type of LAMA (e.g. tiotropium HandiHaler 18 mcg, tiotropium Respimat 5 mcg).
	3. Ergebnisdarstellung Qualitätsbewertung: Overall, included studies showed high methodological quality and were largely given low risk of bias ratings

(1) LAMA add-on vs ICS alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Exacerbations requiring oral corticosteroids	3	2277	Odds Ratio (M-H, Random, 95% CI)	0.65 [0.46, 0.93]
2 Quality of life (AQLQ)	3	1713	Mean Difference (IV, Random, 95% CI)	0.05 [-0.03, 0.12]
3 All-cause serious adverse events	5	2562	Odds Ratio (M-H, Random, 95% CI)	0.60 [0.23, 1.57]
4 Exacerbations requiring hospital admission	5	2562	Odds Ratio (M-H, Random, 95% CI)	0.42 [0.12, 1.47]
5 Trough FEV_1 (litres, change from baseline)	5	2459	Mean Difference (IV, Random, 95% CI)	0.14 [0.10, 0.17]
6 Peak FEV_1 (litres, change from baseline)	3	1923	Mean Difference (IV, Random, 95% CI)	0.19 [0.15, 0.23]
7 Trough PEF (litres/min, change from baseline)	5	2456	Mean Difference (IV, Random, 95% CI)	28.07 [22.51, 33.64]
8 Trough FVC (litres, change from baseline)	4	2002	Mean Difference (IV, Random, 95% CI)	0.09 [0.05, 0.13]
9 Peak FVC (litres, change from baseline)	3	1922	Mean Difference (IV, Random, 95% CI)	0.11 [0.08, 0.15]
10 Asthma control (ACQ)	3	1916	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.19, 0.03]
11 Asthma control (ACQ 'responder')	3	2009	Odds Ratio (M-H, Random, 95% CI)	1.23 [0.87, 1.74]
12 Any adverse events	5	2562	Odds Ratio (M-H, Random, 95% CI)	0.95 [0.80, 1.14]
13 Adverse events classified as asthma	5	2561	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.69, 1.05]

- The rate of exacerbations requiring oral corticosteroids (OCS) was lower in patients prescribed an LAMA add-on than in those receiving the same dose of ICS alone (odds ratio (OR) 0.65, 95% confidence interval (CI) 0.46 to 0.93; 2277 participants; four studies; I2 = 0%; high-quality evidence), meaning that 27 fewer people per 1000 would have an exacerbation over 21 weeks requiring OCS with LAMA compared with ICS alone (95% CI 42 fewer to 6 fewer).
- All-cause serious adverse events (SAEs) and exacerbations requiring hospital admission were rare and the effects too imprecise to permit firm conclusions, but effects suggested that LAMA add-on may be associated with fewer of both compared with ICS alone (SAEs: OR 0.60, 95%CI 0.23 to 1.57; 2532 participants; four studies; low-quality evidence; exacerbations requiring hospital admission: OR 0.42, 95% CI 0.12 to 1.47; 2562 participants; five studies; moderate-quality evidence).
- Additional therapy with a LAMA showed no clear benefit in terms of quality of life compared with ICS given alone
- high-quality evidence showed only a small mean improvement in quality of life as measured on the Asthma Quality of Life Questionnaire (AQLQ), which was not statistically significant. The same was true for asthma control as measured on the Asthma Control Questionnaire (ACQ), which was based on moderate-quality evidence.
- LAMA combined with ICS showed consistent benefit in a range of lung function measures compared with the same dose of ICS alone, and LAMA was not associated with significantly higher rates of adverse events than were reported with placebo.

(2) Subgruppenanalyse

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause serious adverse events - by study duration	5	2562	Odds Ratio (M-H, Random, 95% CI)	0.60 [0.23, 1.57]
1.1 ≤ 6 months	4	2277	Odds Ratio (M-H, Random, 95% CI)	0.87 [0.37, 2.05]
1.2 > 6 months	1	285	Odds Ratio (M-H, Random, 95% CI)	0.19 [0.07, 0.53]
2 Exacerbations requiring oral corticosteroids - by Respimat dose	3	2277	Odds Ratio (M-H, Random, 95% CI)	0.66 [0.46, 0.93]
2.1 Respimat 2.5 mcg	2	1012	Odds Ratio (M-H, Random, 95% CI)	0.53 [0.29, 0.95]
2.2 Respimat 5 mcg	3	1265	Odds Ratio (M-H, Random, 95% CI)	0.74 [0.48, 1.15]
3 Quality of life (AQLQ) - by Respimat dose	3	1713	Mean Difference (IV, Random, 95% CI)	0.05 [-0.03, 0.12]
3.1 Respimat 2.5 mcg	2	734	Mean Difference (IV, Random, 95% CI)	0.04 [-0.08, 0.16]
3.2 Respimat 5 mcg	3	979	Mean Difference (IV, Random, 95% CI)	0.05 [-0.05, 0.15]
4 All-cause serious adverse events - by Respimat dose	5	2717	Odds Ratio (M-H, Random, 95% CI)	0.55 [0.30, 1.03]
4.1 Respimat 2.5 mcg	5	1487	Odds Ratio (M-H, Random, 95% CI)	0.58 [0.22, 1.50]
4.2 Respimat 5 mcg	4	1230	Odds Ratio (M-H, Random, 95% CI)	0.54 [0.21, 1.43]
5 All-cause serious adverse events - by ICS dose	5	2562	Odds Ratio (M-H, Fixed, 95% CI)	0.59 [0.35, 1.00]
5.1 Low-dose ICS	1	464	Odds Ratio (M-H, Fixed, 95% CI)	0.5 [0.03, 8.05]
5.2 Medium-dose ICS	4	2098	Odds Ratio (M-H, Fixed, 95% CI)	0.60 [0.35, 1.01]

4. Anmerkungen/Fazit der Autoren

- Five studies met the inclusion criteria; all were double-blind, double-dummy randomised controlled trials and ranged in length from 12 to 52 weeks.
- Participants in all included studies continued their pre-study maintenance dose of ICS throughout the study period, which ranged from low dose to high dose.
- The rate of exacerbations requiring oral corticosteroids (OCS) was lower in patients prescribed an LAMA add-on than in those receiving the same dose of ICS alone (odds ratio (OR) 0.65, 95% confidence interval (CI) 0.46 to 0.93; 2277 participants; four studies; I^2 =0%; high-quality evidence),
- For adults taking ICS for asthma without a long-acting beta –agonist (LABA), LAMA given as add-on treatment reduces the likelihood of exacerbations requiring treatment with OCS and improves lung function. The benefits of LAMA combined with ICS for hospital admissions, all-cause serious adverse events, quality of life and asthma control remain unknown.

Results of this review, along with findings of related reviews conducted to assess the use of LAMA in other clinical scenarios involving asthma, can help to define the role of LAMA in the management of asthma. Trials of longer duration (up to 52 weeks) would provide a better opportunity to observe rare events such as serious adverse events and exacerbations requiring hospital admission.

Evans DJ et al., 2015 [10].

Long-acting muscarinic antagonists

1. Fragestellung

To compare the effects of adding a LAMA to any dose of ICS versus increasing the dose of ICS, for uncontrolled asthma in adults.

1. Methodik

(LAMA) added to inhaled corticosteroids (ICS) versus higher dose ICS for adults with asthma (Review)	Population: adults (at least 18 years) whose asthma was not well controlled on ICS alone Intervention: ICS + LAMA add-on Komperator: ICS dose increase Endpunkte: (1) primäre Endpunkte: Exacerbations requiring oral corticosteroids; Quality of life (measured on a validated asthma scale, e.g. Asthma Quality of Life Questionnaire, AQLQ); All-cause serious adverse events (2) sekundäre Endpunkte: Exacerbations requiring hospital admission; Lung function (in particular, trough forced expiratory volume in one second (FEV1)); Asthma control (measured on a validated scale, e.g. Asthma Control Questionnaire (ACQ), Asthma Control Test); adverse events Suchzeitraum (Aktualität der Recherche): bis April 2015 Anzahl eingeschlossene Studien/Patienten (Gesamt): 1 RCT Qualitätsbewertung der Studien: Cochrane Risk of Bias Tool; geplante Sensitivitätsanalyse für die primären Endpunkte unter Ausschluss von Studien mit hohem Verzerrungspotential, nicht-publizierten Daten und Cross-over studies Heterogenität: I^2 nach Higgins/Thompson (greater than 30% → they reported it and explored possible causes by pre-specified subgroup analysis) → a priori definierte Subgruppen: • Duration of therapy (≤ 6 months, > 6 months). • Corticosteroid dose in the control group (according to GINA 2014 defined low, medium and high cutoffs). Dose and type of LAMA (e.g. tiotropium Handihaler 18 mcg, tiotropium Respimat 5 mcg).
	3. Ergebnisdarstellung • Nur eine Studie eingeschlossen (Peters et al. 2010) → 210 adult participants with asthma received tiotropium bromide (a LAMA) plus beclomethasone (an ICS); salmeterol xinaoate (LABA) plus beclomethasone, or double-dose beclomethasone, in a randomly assigned order (three-way cross-over design) → **Only the LAMA plus ICS and double ICS groups are relevant to the present review and are considered herein.** Qualitätsbewertung: The included study was of a high methodological quality. Ergebnisse: • Compared with people taking a double dose of ICS, fewer people taking a LAMA add-on had an exacerbation requiring treatment with

	OCS (odds ratio (OR) 0.57, 95% confidence interval (CI) 0.22 to 1.43) or an exacerbation resulting in emergency department admission (OR 0.49, 95% CI 0.09 to 2.77), but the confidence intervals for both outcomes did not exclude the possibility that double dose ICS was more effective. • Serious adverse events and exacerbations requiring hospitalisation occurred in similarly low numbers of people taking each treatment, but confidence intervals were too wide to suggest that the two treatment options were equivalent. • Asthma-related quality of life was similar in both treatment groups (mean difference (MD) in change from baseline 0.10, 95% CI − 0.07 to 0.27). Those taking LAMA add-on scored slightly better on a scale measuring asthma control than those increasing their ICS dose (MD in change from baseline − 0.18, 95% CI − 0.34 to − 0.02), although the difference was clinically small. Evidence was deemed low quality for both quality of life and asthma control. There was moderate-quality evidence that participants' trough forced expiratory volume in one second (FEV1) was 100 mL better when taking LAMA add-on than with increased ICS dose (MD in change from baseline 0.10, 95% CI 0.03 to 0.17).
	4. Anmerkungen/Fazit der Autoren Only one randomised trial was found, comparing tiotropium add-on to increased dose beclomethasone. Differences between the treatments were too small or imprecise to understand whether adding a LAMA to ICS is safer or more effective than increasing the dose of ICS, and there is a possibility of carry-over effects due to the study's cross-over design. LAMA add-on may lead tomore improvement in lung function (FEV1) than an increased dose of ICS. 5. *Kommentare zum Review* • Nur eine Studie
Cates CJ et al., 2014 [8]. Safety of regular formoterol or salmeterol in adults with asthma: an overview of Cochrane reviews	1. Fragestellung To assess the risk of serious adverse events in adults with asthma treated with regular maintenance formoterol or salmeterol compared with placebo, or when randomly assigned in combination with regular ICS, compared with the same dose of ICS.
	2. Methodik <u>Population:</u> Adults and adolescents (over the age of 12 years) with asthma. <u>Intervention/ Komparator:</u> (1) formoterol monotherapy versus placebo. (2) salmeterol monotherapy versus placebo. (3) formoterol in combination with ICS versus the same dose of ICS.

	(4) salmeterol in combination with ICS versus the same dose of ICS. (5) formoterol versus regular salmeterol. (6) formoterol in combination with ICS versus regular salmeterol in combination with ICS. Endpunkte: (1) primäre Endpunkte: death of any cause and adults with one or more non-fatal serious adverse events of any cause (2) sekundäre Endpunkte: asthma-related deaths and adults with one or more asthma-related non-fatal serious adverse events Suchzeitraum (Aktualität der Recherche): bis 2014 Anzahl eingeschlossene Studien/Patienten (Gesamt): 6 Reviews Qualitätsbewertung der Studien: AMSTAR tool; Sensitivity analyses were carried out using risk differences; these gave very similar results to the point estimates derived from the odds ratios models). Heterogenität: I^2 nach Higgins/Thompson Inconsistency between direct and indirect comparisons of formoterol versus salmeterol was assessed by entering pooled results from the trials with direct comparisons and pooled indirect comparisons as separate subgroups Inconsistency between direct and indirect comparisons of formoterol versus salmeterol was assessed by entering pooled results from the trials with direct comparisons and pooled indirect comparisons as separate subgroups → We did not combine the results of direct and indirect comparisons of formoterol and salmeterol, or carry out a network meta-analysis, because of concerns over transitivity assumptions that posed a threat to the validity of indirect comparisons. Hinweis: eingeschlossen wurden **Cochrane reviews**
	3. Ergebnisdarstellung **6 high-quality Reviews** eingeschlossen (all achieved a score of at least nine of a possible 11) → 4 reviews (89 trials with 61,366 adults) related to the safety of regular formoterol or salmeterol as monotherapy or combination therapy; 2 reviews assessed safety from trials in which adults were randomly assigned to formoterol versus salmeterol. These included three trials with 1116 participants given monotherapy (all prescribed background ICS) and 10 trials with 8498 adults receiving combination therapy. An additional search for trials in September 2013 identified **5 new included studies** contributing data from 693 adults with asthma treated with combination formoterol/fluticasone in comparison with the same dose of inhaled fluticasone, as well as from 447 adults for whom formoterol monotherapy was compared with placebo.

Figure 3. Formoterol or salmeterol monotherapy versus placebo (with variable background use of ICS).

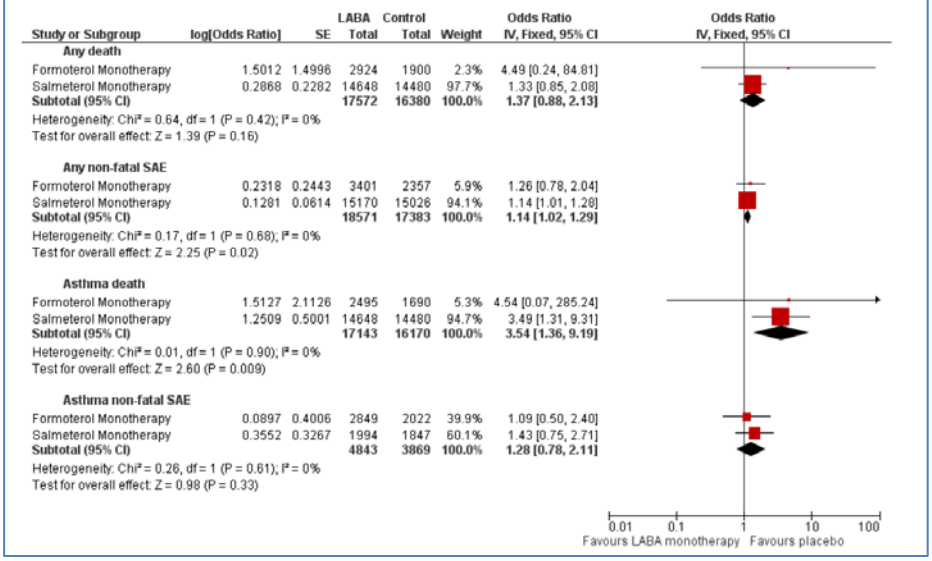


Figure 4. Formoterol monotherapy versus salmeterol monotherapy.

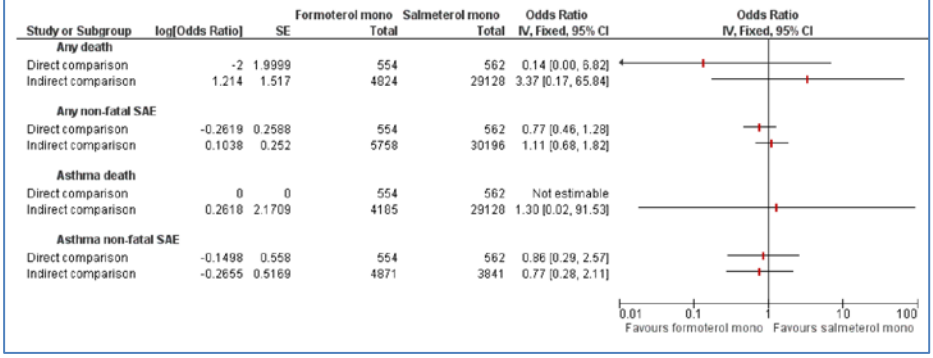


Figure 5. Formoterol or salmeterol combination therapy versus the same dose of ICS.

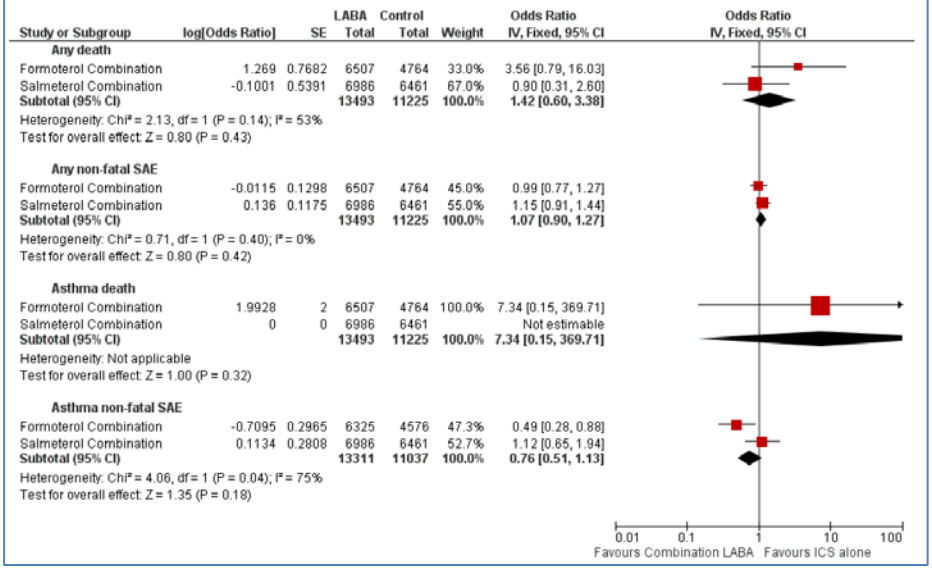
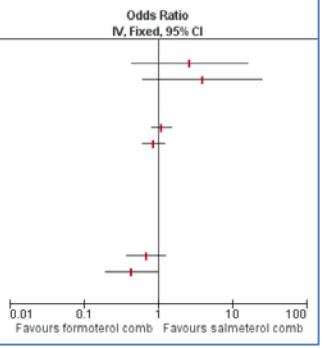


Figure 6. Formoterol combination therapy versus salmeterol combination therapy.

Study or Subgroup	log[Odds Ratio]	SE	Formoterol comb Total	Salmeterol comb Total	Odds Ratio IV, Fixed, 95% CI
Any death					
Direct comparison	0.9848	0.9165	3453	3316	2.68 [0.44, 16.14]
Indirect comparison	1.3691	0.9385	11271	13447	3.93 [0.62, 24.74]
Any non-fatal SAE					
Direct comparison	0.1122	0.159	3453	3316	1.12 [0.82, 1.53]
Indirect comparison	-0.1475	0.1751	11271	13447	0.86 [0.61, 1.22]
Asthma death					
Direct comparison	0	0	3453	3316	Not estimable
Indirect comparison	0	0	11271	13447	Not estimable
Asthma non-fatal SAE					
Direct comparison	-0.3757	0.31	3081	3082	0.69 [0.37, 1.26]
Indirect comparison	-0.823	0.4084	10901	13447	0.44 [0.20, 0.98]



(1) Ergebnisse: Death of any cause

- None of the reviews found a significant increase in death of any cause from direct comparisons; however, none of the reviews could exclude the possibility of a two-fold increase in mortality on regular formoterol or salmeterol (as monotherapy vs placebo or as combination therapy versus ICS) in adults with asthma.
- Pooled mortality results from direct comparisons were as follows: formoterol monotherapy (odds ratio (OR) 4.49, 95% confidence interval (CI) 0.24 to 84.80, 13 trials, N = 4824), salmeterol monotherapy (OR 1.33, 95% CI 0.85 to 2.08, 10 trials, N = 29,128), formoterol combination (OR 3.56, 95% CI 0.79 to 16.03, 25 trials, N = 11,271) and salmeterol combination (OR 0.90, 95% CI 0.31 to 2.6, 35 trials, N = 13,447). In each case, we did not detect heterogeneity, and the quality of evidence was rated as moderate.
- Absolute differences in mortality were very small, translating into an increase of 7 per 10,000 over 26 weeks on any monotherapy (95% CI 2 less to 23 more) and 3 per 10,000 over 32 weeks on any combination therapy (95% CI 3 less to 17 more). Very few deaths were reported in the combination therapy trials, and combination therapy trial designs were different from those of monotherapy trials. Therefore we could not use indirect evidence to assess whether regular combination therapy was safer than regular monotherapy.
- Only one death occurred in the monotherapy trials comparing formoterol versus salmeterol, so evidence was insufficient to compare mortality.

(2) Non-fatal serious adverse events of any cause

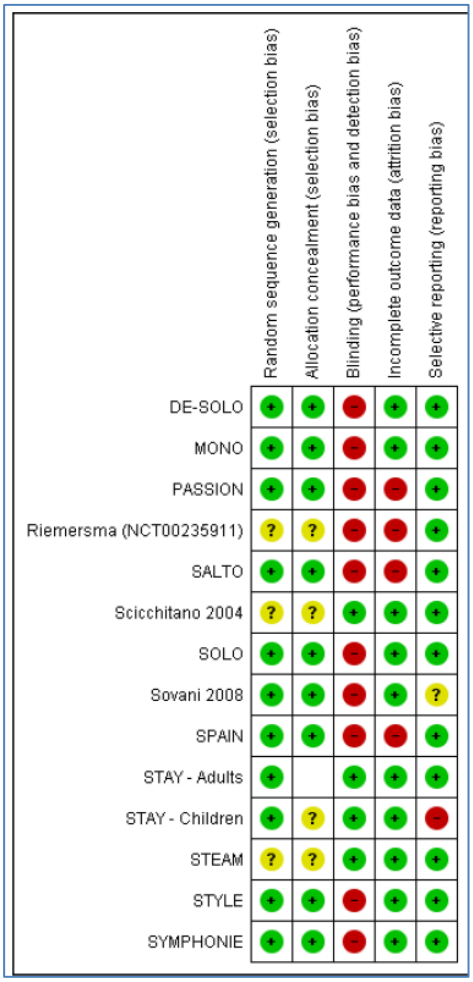
- Direct evidence showed that non-fatal serious adverse events were increased in adults receiving salmeterol monotherapy (OR 1.14, 95% 1.01 to 1.28, I2 = 0%,13 trials, N = 30,196) but were not significantly increased in any of the other reviews: formoterol monotherapy (OR 1.26, 95% CI 0.78 to 2.04, I2 = 15%, 17 trials, N = 5758), formoterol combination (OR 0.99, 95% CI 0.77 to 1.27, I2 = 0%, 25 trials, N = 11,271) and salmeterol combination (OR 1.15, 95% CI 0.91 to 1.44, I2 = 0%, 35 trials, N = 13,447). This represents an absolute increase on any monotherapy of 43 per 10,000 over 26 weeks (95% CI 6 more to 85 more) and 16 per 10,000 over 32 weeks (95% CI 22 less to 60

	more) on any combination therapy. Direct comparisons of formoterol and salmeterol detected no significant differences between risks of all non-fatal events in adults (as monotherapy or as combination therapy).
	4. Anmerkungen/Fazit der Autoren Available evidence from the reviews of randomised trials cannot definitively rule out an increased risk of fatal serious adverse events when regular formoterol or salmeterol was added to an inhaled corticosteroid (as background or as randomly assigned treatment) in adults or adolescents with asthma. An increase in non-fatal serious adverse events of any cause was found with salmeterol monotherapy, and the same increase cannot be ruled out when formoterol or salmeterol was used in combination with an inhaled corticosteroid, although possible increases are small in absolute terms. However, if the addition of formoterol or salmeterol to an inhaled corticosteroid is found to improve symptomatic control, it is safer to give formoterol or salmeterol in the form of a combination inhaler (as recommended by the US Food and Drug Administration (FDA)). This prevents the substitution of LABA for an inhaled corticosteroid if symptom control is improved on LABA. The results of three large ongoing trials in adults and adolescents are awaited; these will provide more information on the safety of combination therapy under less supervised conditions and will report separate results for the adolescents included. 5. *Kommentare zum Review* Hinweis: eingeschlossen wurden **Cochrane reviews**
Kew KM et al., 2013 [24]. Combination formoterol and budesonide as maintenance and reliever therapy versus combination inhaler maintenance for chronic asthma in adults and children	1. Fragestellung To assess the efficacy and safety of budesonide/formoterol in a single inhaler (SiT) to be used for both maintenance and reliever therapy in asthma in comparison with maintenance treatment provided through combination inhalers with a higher maintenance steroid dose (either fluticasone/salmeterol or budesonide/ formoterol), along with additional fast-acting beta2-agonists for relief of symptoms.
	2. Methodik Population: Adults and children with a diagnosis of chronic asthma. Intervention: Any dose of combined budesonide and formoterol delivered through a single inhaler for maintenance and reliever therapy (SiT) Komparator: Combination ICS/LABA inhalers (fluticasone/salmeterol or budesonide/formoterol) at a higher maintenance steroid dose than the maintenance dose in the SiT group, with additional fast-acting beta2-agonist inhaler for symptom relief.

	Endpunkte: (1) primäre Endpunkte: Exacerbations requiring hospitalization; Exacerbations requiring oral corticosteroids; Serious adverse events (including mortality and life threatening events). (2) sekundäre Endpunkte: Severe exacerbations (composite outcome of hospitalisation/ER visit); Diary card morning and evening peak expiratory flow (PEF, L/min); Clinic spirometry (FEV1, mL); Number of rescue medication puffs required per day; Days with symptoms/symptom-free days (%); Nocturnal awakenings (%); Quality of life. Suchzeitraum (Aktualität der Recherche): bis November 2013 Anzahl eingeschlossene Studien/Patienten (Gesamt): 4 Studien Qualitätsbewertung der Studien: Cochrane Collaboration's 'Risk of bias' tool; Sensitivity analysis has been conducted on the basis of risk of bias in studies and baseline severity (based on baseline use of ICS and baseline percentage predicted FEV1). Heterogenität: I^2 nach Higgins/Thompson (When this exceeded 20%, we investigated the possible causes of heterogeneity)
	3. Ergebnisdarstellung Hinweis: All 4 trials included outpatients at least 12 years of age and thus were treated as adult and adolescent studies (N=9130). Qualitätsbewertung: All studies were funded by only one pharmaceutical company (AstraZeneca) and were mostly free from methodological biases, although two studies were rated at high risk for blinding because the inhalers were delivered in an open-label design. Evidence of selective outcome reporting was found in two of the trials, and this is reflected in the grade ratings of the affected outcomes. **Ergebnisse:** • Separate data for exacerbations leading to hospitalisations, to emergency room (ER) visits or to a course of oral steroids could not be obtained. Compared with higher fixed-dose combination inhalers, fewer people using SiT had exacerbations requiring hospitalization or a visit to the ER (odds ratio (OR) 0.72, 95% confidence interval (CI) 0.57 to 0.90; I2 = 0%, P = 0.66), and fewer had exacerbations requiring a course of oral corticosteroids (OR 0.75, 95%CI 0.65 to 0.87; I2 = 0%, P = 0.82). This translates to one less person admitted to hospital or visiting the ER (95% CI 0 to 2 fewer) and two fewer people needing oral steroids (95% CI 1 to 3 fewer) compared with fixed-dose combination treatment with a short-acting beta-agonist (SABA) reliever (per 100 treated over eight months). • No statistical heterogeneity was observed in either outcome, and the evidence was rated of high quality. Although issues with blinding were evident in two of the studies, and one study recruited a less severe population, sensitivity analyses did not change the main results, so

	quality was not downgraded. We could not rule out the possibility that SiT increased rates of serious adverse events (OR 0.92, 95% CI 0.74 to 1.13; I2 = 0%, P = 0.98; moderate-quality evidence, downgraded owing to imprecision). We were unable to say whether SiT improved results for several secondary outcomes (morning and evening peak expiratory flow (PEF), rescue medication use, symptoms scales), and in cases where results were significant, the effect sizes were not considered clinically meaningful (predose FEV1, nocturnal awakenings and quality of life).
	4. Anmerkungen/Fazit der Autoren SiT reduces the number of people having asthma exacerbations requiring oral steroids and the number requiring hospitalisation or an ER visit compared with fixed-dose combination inhalers. Evidence for serious adverse events was unclear. The mean daily dose of inhaled corticosteroids (ICS) in SiT, including the total dose administered with reliever use, was always lower than that of the other combination groups. This suggests that the flexibility in steroid administration that is possible with SiT might be more effective than a standard fixed-dose combination by increasing the dose only when needed and keeping it low during stable stages of the disease. Data for hospitalisations alone could not be obtained, and no studies have yet addressed this question in children younger than age 12. 5. *Kommentare zum Review* In den Studien sind Patienten ab 12 Jahren eingeschlossen
Cates CJ et al., 2013 [7]. Combination formoterol and budesonide as maintenance and reliever therapy versus current best practice (including inhaled steroid maintenance), for chronic asthma in adults and children	1. Fragestellung To assess the efficacy and safety of budesonide and formoterol in a single inhaler for maintenance and reliever therapy in asthma compared with maintenance with inhaled corticosteroids (alone or as part of current best practice) and any reliever therapy.
	2. Methodik Population: Adults and children with a diagnosis of chronic asthma. Intervention: inhaled steroid and long-acting beta2-agonist (LABA) delivered through a single inhaler device for regular maintenance and the relief of asthma symptoms. Komparator: Inhaled corticosteroid given as regular maintenance treatment with a separate reliever inhaler. Endpunkte: (1) primäre Endpunkte: Patients with exacerbations requiring hospitalization; Patients with exacerbations requiring oral corticosteroids; Serious adverse events (including mortality and lifethreatening events); Growth (in children) (2) sekundäre Endpunkte: Severe exacerbations (composite outcome

	of hospitalisation/emergency room (ER) visit/oral steroid course); Diary card morning and evening peak expiratory flow (PEF); Clinic spirometry (FEV1); Number of rescue medication puffs required per day; Symptoms/symptom-free days; Nocturnal awakenings; Quality of life Suchzeitraum (Aktualität der Recherche): bis Februar 2013 Anzahl eingeschlossene Studien/Patienten (Gesamt): 10 studies (21 citations) Qualitätsbewertung der Studien: Cochrane Risk of Bias Tool; geplante Sensitivitätsanalyse were planned on the basis of risk of bias in studies and methods of data analysis (fixed-effect and random-effects models). Heterogenität: I^2 nach Higgins/Thompson (Where this exceeded 20%, we investigated the heterogeneity found, before deciding whether to combine the study results for the outcome) a priori definierte Subgruppen: Adult studies were considered as those that recruited participants from 18 years of age upwards. Adult and adolescent studies were considered as those that recruit participants from 12 years of age upwards. We considered participants in studies where the upper age limit was 12 years as children, and in studies where the upper age limit was 18 years as children and adolescents.
	3. Ergebnisdarstellung Qualitätsbewertung:



Ergebnisse:

(1) Adults and adolescents treated with 160/4.5 µg single inhaler therapy (SiT) (twice daily and as-needed) versus current best practice) (8 Studien)

→ All of these studies ran for six months and recruited participants whose asthma was not controlled in spite of regular inhaled corticosteroids, or who were on treatment with LABA and ICS at recruitment (around 80% of those recruited).

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Patients with exacerbations causing hospitalisation	8	8841	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.81 [0.45, 1.44]
2 Patients with exacerbations treated with oral steroids	8	8841	Odds Ratio (M-H, Fixed, 95% CI)	0.83 [0.70, 0.98]
3 Fatal serious adverse events (fatal)	8	8841	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.95 [0.53, 7.21]
4 Serious adverse events (non-fatal)	8	8839	Odds Ratio (M-H, Fixed, 95% CI)	1.20 [0.90, 1.60]
5 Discontinuation due to adverse events	7	8411	Odds Ratio (M-H, Fixed, 95% CI)	2.85 [1.89, 4.30]
6 Patients with "severe" exacerbation (time to event)	7	7355	Hazard Ratio (Fixed, 95% CI)	0.94 [0.85, 1.04]
7 Change in PEF (% predicted)	1		Mean Difference (Fixed, 95% CI)	Subtotals only
8 Rescue medication use (puffs per day)	1		Mean Difference (Fixed, 95% CI)	Subtotals only
9 Quality of Life (change in ACQ score)	5		Mean Difference (Fixed, 95% CI)	Totals not selected
10 ICS dose (micrograms per day)	5		Mean Difference (Fixed, 95% CI)	Totals not selected
10.1 ICS as prescribed	4		Mean Difference (Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 BDP equivalent doses	1		Mean Difference (Fixed, 95% CI)	0.0 [0.0, 0.0]

- In adults whose asthma was not well-controlled on ICS, the reduction

	in hospital admission with SiT did not reach statistical significance (Peto odds ratio (OR) 0.81; 95% confidence interval (CI) 0.45 to 1.44, eight trials, N = 8841, low quality evidence due to risk of detection bias in open studies and imprecision). The rates of hospital admission were low; for every 1000 people treated with current best practice six would experience a hospital admission over six months compared with between three and eight treated with SiT. • The odds of experiencing exacerbations needing treatment with oral steroids were lower with SiT compared with control (OR 0.83; 95%CI 0.70 to 0.98, eight trials, N = 8841, moderate quality evidence due to risk of detection bias). For every 100 adults treated with current best practice over six months, seven required a course of oral steroids, whilst for SiT there would be six (95% CI 5 to 7). The small reduction in time to first severe exacerbation needing medical intervention was not statistically significant (hazard ratio (HR) 0.94; 95% CI 0.85 to 1.04, five trials, N = 7355). Most trials demonstrated a reduction in the mean total daily dose of ICS with SiT (mean reduction was based on self-reported data from patient diaries and ranged from 107 to 385 µg/day). • Withdrawals due to adverse events were more common in people treated with SiT (OR 2.85; 95% CI 1.89 to 4.30, moderate quality evidence due to risk of detection bias). **(2) Adults treated with 80/4.5 µg single inhaler therapy (SiT) (two doses in the evening and as-needed) versus current best practice (1 Studie)** • The daily average dose of ICS was lower on the SiT arm (326 µg/ day in comparison to 798 µg/day on usual care), but the number of participants with exacerbations and adverse eventswas too small to assess whether the treatments were equivalent or different for the primary outcomes of this review **(4) Adults and adolescents treated with single inhaler therapy (SiT) versus maintenance inhaled corticosteroids (ICS) with separate reliever inhaler (4 Studien)**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Patients with exacerbations causing hospitalisation	3	4209	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.56 [0.28, 1.09]
1.1 Single inhaler therapy versus higher dose ICS	3	4209	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.56 [0.28, 1.09]
2 Patients with exacerbations treated with oral steroids	4	4280	Odds Ratio (M-H, Fixed, 95% CI)	0.54 [0.45, 0.64]
2.1 Single inhaler therapy versus higher dose ICS	3	4209	Odds Ratio (M-H, Fixed, 95% CI)	0.53 [0.44, 0.63]
2.2 Single inhaler therapy versus same dose ICS	1	71	Odds Ratio (M-H, Fixed, 95% CI)	1.42 [0.29, 6.86]
3 Fatal serious adverse events	3	4209	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.37 [0.05, 2.62]
3.1 Single inhaler therapy versus higher dose ICS	3	4209	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.37 [0.05, 2.62]
4 Serious adverse events (non-fatal)	3	4209	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.73, 1.29]
4.1 Single inhaler therapy versus higher dose ICS	3	4209	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.73, 1.29]
5 Discontinuation due to adverse events	2	2586	Odds Ratio (M-H, Fixed, 95% CI)	0.57 [0.35, 0.93]
5.1 Single inhaler therapy versus higher dose ICS	2	2586	Odds Ratio (M-H, Fixed, 95% CI)	0.57 [0.35, 0.93]
6 Patients with "severe" exacerbation (time to event)	2	2586	Hazard Ratio (Fixed, 95% CI)	0.59 [0.49, 0.70]
6.1 Single inhaler therapy versus higher dose ICS	2	2586	Hazard Ratio (Fixed, 95% CI)	0.59 [0.49, 0.70]
7 PEF (Litres/min)	3		Mean Difference (Fixed, 95% CI)	22.29 [17.62, 26.95]
7.1 Single inhaler therapy versus higher dose ICS	3		Mean Difference (Fixed, 95% CI)	22.29 [17.62, 26.95]
8 FEV_1 increase (Litres)	3		Mean Difference (Fixed, 95% CI)	0.10 [0.07, 0.13]
8.1 Single inhaler therapy versus higher dose ICS	2		Mean Difference (Fixed, 95% CI)	0.10 [0.08, 0.13]
8.2 Single inhaler therapy versus same dose ICS	1		Mean Difference (Fixed, 95% CI)	0.01 [-0.19, 0.21]
9 Rescue medication use (puffs per day)	3		Mean Difference (Fixed, 95% CI)	-0.37 [-0.49, -0.25]
9.1 Single inhaler therapy versus higher dose ICS	3		Mean Difference (Fixed, 95% CI)	-0.37 [-0.49, -0.25]
10 Quality of Life (fall in ACQ score)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
10.1 Single inhaler therapy versus same dose ICS	1		Mean Difference (Fixed, 95% CI)	0.0 [0.0, 0.0]

- Three studies including 4209 adults compared SiT with higher dose budesonide maintenance and terbutaline for symptom relief. The studies were considered as low risk of bias. The run-in for these studies involved withdrawal of LABA, and patients were recruited who were symptomatic during run-in. The reduction in the odds of hospitalisation with SiT compared with higher dose ICS did not reach statistical significance (Peto OR; 0.56; 95% CI 0.28 to 1.09, moderate quality evidence due to imprecision).
- Fewer patients on SiT needed a course of oral corticosteroids (OR 0.54; 95% CI 0.45 to 0.64, high quality evidence). For every 100 adults treated with ICS over 11 months, 18 required a course of oral steroids, whilst for SiT there would be 11 (95% CI 9 to 12).

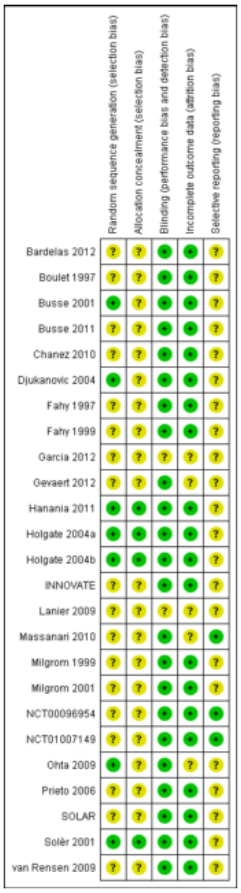
Withdrawals due to adverse events were more common in people treated with SiT (OR 0.57; 95% CI 0.35 to 0.93, high quality evidence).

4. Anmerkungen/Fazit der Autoren

Guidelines suggest the addition of regular LABA or increasing the dose of ICS for asthma that is not controlled on regular low dose ICS. SiT did not significantly reduce exacerbations leading to hospitalisation in comparison with current best practice. However, SiT can reduce the risk of asthma exacerbations needing oral corticosteroids in comparison with fixed dose maintenance ICS, and to a lesser degree in comparison with current best

	practice in adults who were not well controlled on regular corticosteroids. There were more discontinuations due to adverse events on SiT compared with current best practice, but no significant differences in fatal or non-fatal serious adverse events. Our confidence in these conclusions is limited by the open-label design of the trials that compared SiT with current best practice, and by the reliability of the self-reporting of adherence to treatment in the trials. The main limitation of the results from studies comparing SiT with higher dose inhaled steroids was the possible selection of participants with diminished asthma control following the withdrawal of LABA during run-in. SiT is not currently licensed for children under 18 years of age in the United Kingdom and there is currently very little research evidence for this approach in children or adolescents. 6. *Kommentare zum Review* • All of the included studies were sponsored or supported by AstraZeneca, the manufacturers of Symbicort.z.T. sind in den Studien Patienten ab 12 Jahren eingeschlossen
Normansell R et al., 2014 [33]. Omalizumab for asthma in adults and children	1. Fragestellung To assess the effects of omalizumab versus placebo or conventional therapy for asthma in adults and children.
	2. Methodik Population: Adults and children with chronic asthma fromall referral sources. Intervention: Anti-IgE therapy at any dose or route Komparator: placebo Endpunkt: primary: 1. Asthma exacerbations as defined by “events”, i.e. hospital admissions, emergency room visits, days lost from work/school, unscheduled doctor visits, increase in medication. 2. Reduction or termination of steroid (inhaled, oral, both) use from baseline or run-in period; secondary: 1. Asthma symptoms, 2. Health-related quality of life, 3. Rescue medication use, 4. Measures of lung function: forced expiratory volume in one second (FEV1), peak expiratory flow (PEF), 5. Adverse events. Recherche: until 06/2013 Anzahl eingeschlossene Studien/Patienten (Gesamt): 25 studies (6382 patients) Qualitätsbewertung der Studien: *Cochrane Handbook for Systematic Reviews of Interventions for assessing the risk of bias in eligible studies*
	3. Ergebnisdarstellung

Qualität der Studien: The evidence presented in this review is generally of moderate quality. Most of the studies did not clearly explain how investigators decided which people would receive omalizumab and which would receive placebo, and this decision is an important part of well-conducted studies.



Summary of findings fort he main comparison

Subcutaneous omalizumab + steroid versus placebo + steroid (stable steroid) for asthma in adults and children

Patient or population: adults and children with asthma
Settings:
Intervention: subcutaneous omalizumab + steroid versus placebo + steroid (stable steroid)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Subcutaneous omalizumab+ steroid versus placebo + steroid (stable steroid)				
Number of participants with at least one exacerbation All asthmatic participants (16 to 60 weeks)	262 per 1000	163 per 1000 (130 to 176)	OR 0.55 (0.46 to 0.65)	3261 (10 studies)	⊕⊕⊕○ **moderate**[1]	
Number of participants with at least one exacerbation Moderate to severe asthma (16 to 60 weeks)	274 per 1000	159 per 1000 (137 to 185)	OR 0.5 (0.42 to 0.6)	2889 (7 studies)	⊕⊕⊕○ **moderate**[1]	
Number of participants with at least one exacerbation Severe asthma (16 to 32 weeks)	145 per 1000	145 per 1000 (78 to 252)	OR 1 (0.5 to 1.99)	277 (2 studies)	⊕⊕○○ **low**[2]	
Mortality 16 to 60 weeks	2 per 1000	0 per 1000 (0 to 3)	OR 0.19 (0.02 to 1.67)	4245 (9 studies)	⊕⊕○○ **low**[3,4]	
Hospitalisations 28 to 60 weeks	31 per 1000	5 per 1000 (2 to 13)	OR 0.16 (0.06 to 0.42)	1824 (4 studies)	⊕⊕⊕○ **moderate**[5]	
Adverse event-serious 16 to 60 weeks	64 per 1000	47 per 1000 (37 to 58)	OR 0.72 (0.57 to 0.91)	5713 (15 studies)	⊕⊕⊕○ **moderate**[6]	

*The basis for the **assumed risk** is the mean control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio.

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] A point was deducted for risk of bias to reflect the fact that most studies scored UNCLEAR on both sequence generation and allocation concealment.
[2] A point was deducted for risk of bias to reflect the fact that only one of the two trials scored LOW on both sequence generation and allocation concealment. The remaining trial scored UNCLEAR on both sequence generation and allocation concealment. An additional point was deducted because of the imprecision of the results.
[3] A point was deducted for risk of bias to reflect the fact that only two of the nine trials scored LOW on both sequence generation and allocation concealment. Most (five) scored UNCLEAR on both sequence generation and allocation concealment.
[4] An additional point was deducted to reflect that a death occurred in only two of the nine trials; therefore, the contribution of most of the trials (seven) was non-estimable.
[5] A point was deducted for risk of bias to reflect the fact that only one of the four trials scored LOW on both sequence generation and allocation concealment.
[6] A point was deducted for risk of bias to reflect the fact that only two of the 15 trials scored LOW on both sequence generation and allocation concealment. Most (10) scored UNCLEAR on both sequence generation and allocation concealment.

Primary outcomes:

1. Asthma exacerbations

- Treatment with omalizumab resulted in fewer exacerbations overall. This effect was maintained during the steroid stable and steroid reduction phases of the included trials but with much greater uncertainty when only participants with severe disease were considered.

2. Steroid withdrawal/reduction

- Participants treated with omalizumab were significantly more likely to be able to reduce and completely withdraw their inhaled corticosteroids. For the subset of participants receiving oral corticosteroids, we remain uncertain whether benefit is derived fromomalizumab over placebo for those withdrawing or reducing their steroid treatment.

	Secondary outcomes: 1. Asthma symptoms • Treatmentwithomalizumabgenerally improvedasthma symptomscores in both steroid stable and steroid reduction phases. 2. Health-related quality of life • In most trials reporting quality of life, a significant benefit of omalizumab over placebo was reported during both steroid stable and steroid reduction phases. 2. Rescue medication use Participants were more likely to be able to reduce their rescue medication when using omalizumab. 4. Measures of lung function • Improvements in lung function were inconsistent across the trials analysed, and the range of different measures presented in the trials prevented meaningful meta-analysis. 5. Adverse events including withdrawals and mortality • Participants receiving subcutaneous omalizumab experienced significantly fewer serious adverse events compared with those given placebo. However, they also experienced significantly more injection site reactions.No significant difference inmortality was detected.
	4. Anmerkungen/Fazit der Autoren Omalizumab was effective in reducing asthma exacerbations and hospitalisations as an adjunctive therapy to inhaled steroids and during steroid tapering phases of clinical trials. Omalizumab was significantly more effective than placebo in increasing the numbers of participants who were able to reduce or withdraw their inhaled steroids. Omalizumab was generally well tolerated, although more injection site reactions were seenwith omalizumab. Further assessment in paediatric populations is necessary, as is direct double-dummy comparison with ICS. Although subgroup analyses suggest that participants receiving prednisolone had better asthma control when they received omalizumab, it remains to be tested prospectively whether the addition of omalizumab has a prednisolone-sparing effect. It is also not clear whether there is a threshold level of baseline serum IgE for optimum efficacy of omalizumab. Given the high cost of the drug, identification of biomarkers predictive of response is of major importance for future research.

Systematische Reviews

Cabon Y et al., 2017 [3]. Comparison of anti-interleukin-5 therapies in patients with severe asthma: global and indirect meta-analyses of randomized placebo controlled trials *Siehe auch:* Wang FP et al., 2016 [40]. Wang FP et al., 2016 [39].	1. Fragestellung Inconsistent results have been reported regarding IL-5 blockade treatment in asthma. There were no direct between-treatment comparisons.
	2. Methodik 1) A meta-analysis was first conducted to assess the efficacy of the IL-5 blockade strategy overall 2) An indirect network meta-analysis was then performed to compare each anti-IL5 mAb efficacy and safety result using the Bayesian framework according to Cochrane's collaboration guidelines *Hinweis*: Further eosinophilic subgroup analysis and sensitivity analysis were also conducted in case of heterogeneity. Population: patients with severe asthma Intervention: anti-interleukin-5 therapies (benralizumab, reslizumab and mepolizumab) Komparator: Placebo (als Brückenkomparator) Endpunkte: annual exacerbation rates, FEV1 change from baseline and variations in asthma symptoms assessed by changes in the ACQ-5 Suchzeitraum (Aktualität der Recherche): from 1990 to September 2015 Anzahl eingeschlossene Studien/Patienten (Gesamt): Of the 11 clinical trials identified, 10 were considered eligible for the meta-analysis, reported in six separate publications and two publications describing two different trials each (total: 3421 patients) Qualitätsbewertung der Studien: Metaanalyse: Cochrane tool / NMA: R-AMSTAR criteria were assessed to check the overall data quality.
	3. Ergebnisdarstellung **Metaanalyse**: • The annual exacerbation rate ratio of the three aggregated anti-IL-5 mAbs vs. placebo was 0.60 [0.50, 0.71], P < 0.01. This effect was assessed by a random effect model due to heterogeneity (I^2 = 0.61). • The heterogeneity noted in the exacerbation rate ratios was due to the combined rate reduction in eosinophilic and non-eosinophilic 2014 Castro's studies. When these two trials were excluded, the exacerbation rate estimates based on the fixed effect model were 0.52 [0.45, 0.60] (P < 0.01, I^2 = 0). • The FEV1 change from baseline vs. placebo was 0.09 L [0.05; 0.12], P < 0.01, using a fixed effect model (I^2 = 0.28).

	• The meta-analysis indicated an overall ACQ-5 change from baseline of -0.31 [-0.41, -0.21], P < 0.01, based on a fixed effect model (I^2 = 0.11) involving seven studies only, because of missing values in three studies. *<u>Subgruppenanalyse</u>:* • A specific meta-analysis was performed in the eosinophilic patient subgroup (> 300 mm3/L). For this subgroup, including five studies, the annual exacerbation rate ratio was 0.57 [0.47, 0.69], P < 0.01, I2 = 0.54. FEV1 increased by 0.10 L [0.06, 0.14] (P < 0.01, I^2 = 0) in this subgroup. ACQ-5 changed by -0.33 [-0.45, -0.21] (P < 0.01, I^2 = 0.21). **Netzwerkemetaanalyse**: • Accordingly, the top three treatments with the greatest probability of being ranked first for reducing the exacerbation rate were reslizumab 3 mg/kg with P1 = 51%, followed by mepolizumab 750 mg (P1 = 22%) and mepolizumab 100 mg (P1 = 13%). Corresponding rate ratio reductions regarding the exacerbation rate vs. placebo were 0.46 [0.3, 0.69] for reslizumab 3 mg/kg, 0.51 [0.35, 0.77] for mepolizumab 750 mg and 0.55 [0.37, 0.83] for mepolizumab 100 mg. As expected, benralizumab 2 mg did not significantly differ from placebo. • Regarding the asthma control questionnaire (ACQ-5) findings, benralizumab 20 mg had the greatest probability of being ranked first (mean difference vs. placebo -0.38 [-0.97, 0.18], P1 = 27%). Reslizumab 3 mg/kg (0.14 L [0.05, 0.24], P1 = 37%) had the best likelihood of being ranked first for FEV1 improvement. Regarding safety concerns, we analysed non-severe adverse events first. Benralizumab 20 mg had the greatest probability of being ranked as the safest (RR = 0.94 [0.57, 1.54], P1 = 28%), which was also in favour of the treatment. For severe adverse events, reslizumab was ranked as the best SAE reducer compared to placebo (RR = 0.81 [0.22, 3.03], P1 = 37%), again in favour of the treatment. *<u>Subgruppenalanyse</u>:* • In the eosinophilic subgroup, the top three drugs for exacerbation rate reduction were reslizumab 3 mg/kg with a 0.46 [0.26, 0.81] rate ratio regarding the annual exacerbation rate vs. placebo, with a probability of being the best treatment P1 = 41%. • This treatment was followed by mepolizumab 750 mg with 0.49 [0.23, 1.02] (P1 = 27%) vs. placebo, and then mepolizumab 100 mg with a 0.54 [0.31, 0.97] (P1 = 11%) rate ratio regarding the annual exacerbation rate vs. placebo. On average, benralizumab 20 mg had the highest probability of being the best treatment for improving the FEV1 value (0.15L [0.30, 0.60], P1 = 29%) and decreasing the ACQ-5 score (-0.36 [-2.28, 1.56], P1 = 18%).

	4. Fazit der Autoren: In conclusion, anti-IL-5 treatment had significant effects in severe asthma patients with frequent exacerbations and evidence of eosinophilic inflammation. Reslizumab appeared to be the most effective mAb in reducing exacerbation rates and improving FEV1. Nonetheless, mepolizumab 100 mg and benralizumab 20 mg appeared to be excellent alternatives. No clear significant differences between treatments in terms of efficacy and safety were found due to the limited number of studies available. Long-term effects, best duration of treatment and the risk of relapse after withdrawal are important issues that should be addressed in further studies. A clear definition of the satisfactory clinical response and the ideal response time for its assessment would also be warranted.
Cockle SM et al., 2017 [9]. Comparative effectiveness of mepolizumab and omalizumab in severe asthma: An indirect treatment comparison	1. Fragestellung To collect all publicly available RCTs to support an **<u>indirect treatment comparison</u>** of mepolizumab and omalizumab in severe asthma.
	2. Methodik Bayesian network meta-analysis <u>Population:</u> patients ≥12 years of age, with severe asthma (patients receiving >1000 mg/day beclomethasone dipropionate equivalent plus ≥1 additional controller, and with a documented history of exacerbations). This population definition was then further refined to incorporate treatment eligibility for mepolizumab and omalizumab, as far as data availability allowed. Two populations were defined, 1) the Overlap population, which aimed to include patients eligible for both mepolizumab AND omalizumab, and 2) the Trial population, which aimed to include patients eligible for either mepolizumab OR omalizumab <u>Intervention:</u> mepolizumab and omalizumab <u>Komparator:</u> placebo, in addition to SoC <u>Endpunkte:</u> • Primary pre-specified endpoints were the rate of clinically significant exacerbations and the rate of exacerbations requiring hospitalization. • Pre-specified secondary endpoints included the change from baseline in health-related quality of life (HRQoL), measured by the St George's Respiratory Questionnaire or Asthma Quality of Life Questionnaire; change from baseline in lung function (FEV1), or postbronchodilator FEV1, or FEV1% predicted, or morning peak expiratory flow (PEF; L/min) when these data were unavailable; change from baseline in asthma control measured by the Asthma Control Questionnaire; and the proportion of patients with any adverse events (AEs), serious AEs (SAEs), withdrawals due to AEs or fatal AEs

	Suchzeitraum (Aktualität der Recherche): A systematic literature review was conducted on August 5, 2014, and updated on July 8, 2015 Anzahl eingeschlossene Studien/Patienten (Gesamt): The systematic literature review identified seven mepolizumab publications corresponding to three distinct RCTs and 29 omalizumab publications, corresponding to 19 distinct RCTs Qualitätsbewertung der Studien: The quality of RCTs was evaluated based on criteria outlined in Supplementary Appendix A (eigene Kriterien)
	3. Ergebnisdarstellung • In the Overlap population, no differences between treatments in clinically significant exacerbations and exacerbations requiring hospitalization were found, although trends favored mepolizumab. • In the Trial population, mepolizumab treatment produced greater reductions in clinically significant exacerbations (RR:0.63 [95% CrI:0.45,0.89]) but not exacerbations requiring hospitalization compared with omalizumab, although the trend favored mepolizumab. Both treatments had broadly comparable effects on lung function, and similar tolerability profiles.
	4. Fazit der Autoren: *In summary, this ITC compared the efficacy and tolerability of mepolizumab and omalizumab. Restrictions in terms of data availability led to a number of study limitations, which have been acknowledged and which were partially tested by additional scenarios and sensitivity analyses. These additional analyses supported the results from the primary analysis, which suggested that in patients with severe asthma eligible to receive both treatments, mepolizumab seems to be at least as efficacious as omalizumab at reducing exacerbations and improving lung function, and that the tolerability profiles of the two treatments do not seem to meaningfully differentiate.* 5. Kommentar zum Review: • This study was funded by GlaxoSmithKline • asthma control and HRQoL could not be included in the analysis; different measures were used in the mepolizumab and omalizumab trials, preventing comparison • differences in the length of time between clinical visits may influence patient recall of AEs, and the existence of an extension study for the mepolizumab population may have influenced the rate of withdrawals average patient age was greater in the mepolizumab MENSA trial (~50 years of age) than in the omalizumab INNOVATE and EXTRA trials (43e45 years of age). consequently, the number of asthma comorbidities in these patients may have differed, suggesting that the comparison of treatment AE profiles between RCTs should be

	interpreted with caution.
CADTH, 2016 [4]. Mepolizumab (Nucala)	1. Fragestellung • To perform a systematic review of the beneficial and harmful effects of mepolizumab for the treatment of adult patients (≥ 18 years) with SEA (≥ 150 cells/mcL at treatment initiation or ≥ 300 cells/mcL in the past 12 months) whose symptoms are inadequately controlled with high-dose ICS and one or more additional asthma controllers.

	2. Methodik
	• Population: For the add-on maintenance treatment of adult patients with severe eosinophilic asthma who:
	  • are inadequately controlled with high-dose inhaled corticosteroids and an additional asthma controller(s) (e.g., LABA), and
	  • have a blood eosinophil count of ≥ 150 cells/mcL (0.15 GI/L) at initiation of treatment with mepolizumab OR ≥ 300 cells/mcL (0.3 GI/L) in the past 12 months.
	Intervention: Mepolizumab 100 SC mg every 4 weeks, as add-on therapy to a high-dose ICS and an additional asthma controller(s)
	Komparator: LABA, LTRA, LABA + LAMA, LABA + LTRA, Omalizumab Chronic OCS
	ICS would be used in combination with all medications. Rescue medication (e.g., SABA, SAMA) may be used for acute exacerbations.
	Endpunkt: Key efficacy outcomes: Health care resource use (i.e., hospitalizations, ED visits, MD visits, Acute asthma exacerbations, Use of OCSa, Quality of life as measured by a validated scalea, Days of missed school or worka, Change in pulmonary function (e.g., PEF, FEV1); Other efficacy outcomes: Symptom reduction (e.g., ACQ), Change in number of asthma symptom–free days or nights, Incidence of nocturnal awakenings, Reduction of use of ICS, Reduction of use of rescue medication; Harms outcomes: AEs, SAEs, WDAEs, Notable harms/harms of special interest: cardiovascular AEs, opportunistic infection, injection-site reactions, malignancies, systemic allergic reactions
	Recherche: until 01/2016
	Anzahl eingeschlossene Studien/Patienten (Gesamt): 2 RCTs (711 patients)
	Qualitätsbewertung der Studien: k. A.

	3. Ergebnisdarstellung Two international, manufacturer-sponsored, phase 3, double-blind, placebo-controlled randomized trials met the inclusion criteria for this

	systematic review. MENSA (N = 576) was a 32-week study that evaluated the efficacy and safety of mepolizumab 100 mg SC and mepolizumab 75 mg IV once every four weeks as adjunctive therapy in patients with SEA. SIRIUS (N = 135) was a 24-week corticosteroid- sparing study that evaluated the effect of mepolizumab 100 mg SC once every four weeks in reducing OCS use in patients with SEA. Both studies enrolled patients at least 12 years of age with documented asthma meeting specific peripheral blood eosinophil counts (≥ 150 cells/mcL at visit 1 or ≥ 300 cells/mcL in the past 12 months) who were on regular treatment with high-dose ICS and an additional controller medication (e.g., LABA, leukotriene receptor antagonist, theophylline). In SIRIUS, eligible patients were to be using OCS at a dose between 5 mg/day and 35 mg/day. The primary end point in MENSA was the rate of clinically significant exacerbations (requiring systemic corticosteroids, hospitalization, or emergency department visits) at week 32. The primary end point in SIRIUS was the percentage reduction of OCS dose during weeks 20 to 24 compared with baseline dose while maintaining asthma control. Patients who completed the MENSA and SIRIUS trials had the option of participating in a 12- month open-label safety study (MEA115661, N = 651), where all patients received mepolizumab 100 mg SC once every four weeks (APPENDIX 6). A phase 2/3 study (DREAM, N = 616) evaluated the efficacy and safety of various IV doses of mepolizumab and is summarized in APPENDIX 7. As the Health Canada–approved dose for mepolizumab is 100 mg SC once every four weeks, only trials that included this dosing regimen were included in this review. Limitations of MENSA and SIRIUS included the relatively short duration of the studies to evaluate asthma exacerbations, the potential for improved compliance to background therapy in a clinical trial setting compared with real life as evidenced by improvements in the placebo groups, and the uncertainty regarding appropriate selection criteria to identify SEA patients.

	MENSA (MEA115588)		SIRIUS (MEA115575)	
	Mepolizumab 100 mg SC (n = 194)	Placebo (n = 191)	Mepolizumab 100 mg SC (n = 69)	Placebo (n = 66)
Clinically Significant Exacerbations — MENSA Primary End Point				
Number of patients, n (%)	64 (33)	105 (55)	29 (42)	45 (68)
Number of exacerbations	116	216	47	68
Exacerbation rate/year	0.83	1.74	1.44	2.12
Rate ratio (95% CI), *P* value[a]	0.47 (0.35 to 0.64), < 0.001		0.68 (0.47 to 0.99)	
Exacerbations Requiring Hospitalization or ED Visit				
Number of patients, n (%)	11 (6)	24 (13)	3 (4)	7 (11)
Number of exacerbations	20	33	3	9
Exacerbation rate/year	0.08	0.20	–[b]	–
Rate ratio (95% CI), *P* value[a]	0.39 (0.18 to 0.83), *P* = 0.015		–[b]	
Exacerbations Requiring Hospitalization				
Number of patients, n (%)	5 (3)	13 (7)	0	7 (11)
Number of exacerbations	9	18	0	8
Exacerbation rate/year	0.03	0.10	–[b]	–
Rate ratio (95% CI), *P* value[a]	0.31 (0.11 to 0.91), *P* = 0.034[c]		–[b]	
Reduction From Baseline in OCS Dose, n (%) – SIRIUS Primary End Point				
OR vs. placebo (95% CI), *P* value[d]	NA	NA	2.39 (1.25 to 4.56), *P* = 0.008	
≥ 50% Reduction in Daily OCS Dose, n (%)				
OR vs. placebo (95% CI), *P* value[d]	NA	NA	2.26 (1.10 to 4.65), *P* = 0.027	
Reduction in Daily OCS Dose to ≤ 5 mg, n (%)				
OR vs. placebo (95% CI), *P* value[d]	NA	NA	2.45 (1.12 to 5.37), *P* = 0.025	
Total Reduction in OCS Dose, n (%)				
OR vs. placebo (95% CI), *P* value[d]	NA	NA	1.67 (0.49 to 5.75), *P* = 0.414	
Median Percentage Reduction in Daily OCS Dose (%)				
Mean difference (95% CI), *P* value[e]			−30.0 (−66.7 to 0.0), *P* = 0.007	
Pre-bronchodilator FEV_1, mL				
Baseline mean (SD)	1,730 (659.2)	1,860 (630.8)	1,897 (660.2)	2,005 (822.3)
LS mean change (SE)	183 (31.1)	86 (31.4)	111 (55.1)	−4 (56.5)
Difference (95% CI), *P* value[a]	98 (11 to 184), *P* = 0.028[f]		114 (−42 to 271)	
Morning PEF, L/min				
Baseline mean (SD)	255.3 (107.6)	277.0 (105.5)	284.7 (124.8)	311.9 (152.3)
Mean change from baseline (SD)	29.5 (69.0)	1.8 (58.9)	19.1 (56.2)	4.1 (47.0)
SGRQ Total Score				
Baseline mean (SD)	47.9 (19.5)	46.9 (19.8)	49.6 (17.8)	45.0 (18.4)
LS mean change (SE)	−16.0 (1.1)	−9.0 (1.2)	−8.8 (1.7)	−3.1 (1.7)
Difference (95% CI), *P* value[a]	−7.0 (−10.2 to −3.8), *P* < 0.001[f]		−5.8 (−10.6 to −1.0)	
≥ 4 point improvement, n (%)	137 (71)	105 (55)	40 (58)	27 (41)
ACQ-5 Total Score				
Baseline mean (SD)	2.26 (1.27)	2.28 (1.19)	2.15 (1.27)	1.99 (1.18)
LS mean change (SE)	−0.94 (0.07)	−0.50 (0.07)	−0.61 (0.13)	−0.09 (0.13)
Difference (95% CI)[a]	−0.44 (−0.63 to −0.25)		−0.52 (−0.87 to −0.17)	
Harms				
Patients with > 0 AEs, n (%)	152 (78)	158 (83)	57 (83)	61 (92)
Patients with > 0 SAEs, n (%)	16 (8)	27 (14)	1 (1)	12 (18)
Patients with > 0 WDAEs, n (%)	1 (< 1)	4 (2)	3 (4)	3 (5)
Notable Harms, n (%)				
Injection-site reaction	17 (9)	6 (3)	4 (6)	2 (3)
Systemic allergic reaction	3 (2)	4 (2)	4 (6)	3 (5)
Serious infection	6 (3)	5 (3)	1 (1)	4 (6)
Opportunistic infection	3 (2)	0	0	1 (2)
Cardiac disorder	4 (2)	5 (3)	2 (3)	3 (5)
Malignancy	0	0	0	3 (5)

	4. Anmerkungen/Fazit der Autoren Two international, manufacturer-sponsored, phase 3, double-blind, placebo-controlled, randomized controlled trials met the inclusion criteria for this systematic review. MENSA (N = 576) was a 32-week study that evaluated the efficacy and safety of mepolizumab 100 mg SC and mepolizumab 75 mg IV once every four weeks as adjunctive therapy in patients with SEA. SIRIUS (N = 135) was a 24-week corticosteroid-sparing study that evaluated the effect of mepolizumab 100 mg SC once every four weeks in reducing OCS use in patients with SEA. Results from MENSA suggested that mepolizumab 100 mg SC is associated with a statistically significant reduction in the rate of clinically significant asthma exacerbations compared with placebo in patients currently on high-dose ICS and an additional asthma controller meeting screening eosinophil criteria of ≥ 150 cells/mcL at screening or ≥ 300 cells/mcL in the past year. Results from SIRIUS suggested that mepolizumab 100 mg SC is associated with a greater likelihood of a reduction in daily OCS dose compared with placebo in patients with SEA who were taking OCS at a dose of 5 mg/day to 35 mg/day. Due to the increased number of exacerbations in the placebo groups compared with the mepolizumab groups, there was greater unplanned health resource use and OCS use in the placebo groups. AE data were generally similar between groups, except for a higher proportion of patients in the placebo groups experiencing asthma-related AEs than in the mepolizumab groups. Safety results from Study MEA115666, a 52-week open-label extension study of patients completing MENSA and SIRIUS, were similar to the AE profile observed in the individual studies. There were no direct head-to-head trials of mepolizumab and other therapies for severe asthma identified in this review. The manufacturer submitted an ITC to evaluate the relative efficacy of mepolizumab and omalizumab in patients with severe asthma who would be eligible for both therapies.
Rodrigo GJ et al., 2016 [36]. Once-daily fluticasone furoate and vilanterol for adolescents and adults with symptomatic asthma	1. Fragestellung The objective of this systematic review was to assess the efficacy and safety of fluticasone furoate-vilanterol compared with ICS monotherapy or twice daily ICS-LABA formulations.
	2. Methodik <u>Population:</u> patients with asthma (12 years or older) with documented use of an ICS with or without a LABA <u>Intervention/ Komperator:</u> comparison of Fluticasone furoate evilanterol with ICS monotherapy or ICS-LABA twice-daily combinations <u>Endpunkte:</u> pulmonary function (forced expiratory volume in 1 second [FEV1] or peak expiratory flow rate [PEF]) as a primary outcome, rescue medication use, health status (Asthma Quality of Life Questionnaire

[AQLQ] total score16), asthma control, number of patients with at least 1 severe asthma exacerbation (defined as a deterioration of asthma requiring the use of systemic corticosteroids for ≥3 days or a hospitalization or emergency department visit due to asthma), withdrawals, and safety of treatment (adverse events [AEs], serious adverse events [SAEs], cardiac events, and pneumonia). A SAE was defined as any untoward medical occurrence that sometimes results in death, is life-threatening, requires inpatient hospitalization, or results in persistent or significant disability or incapacity.

Suchzeitraum (Aktualität der Recherche): bis Januar 2016
Anzahl eingeschlossene Studien/Patienten (Gesamt): 7 RCTs (n=5,668)

Qualitätsbewertung der Studien: risk of bias assessment according to recommendations outlined in the Cochrane Handbook
Heterogenität: Statistical heterogeneity was measured by the I2 test (<25% absence, 26%-39% unimportant, 40%-60% moderate, and 60%-100% substantial).

Subruppen: a priori subgroup analysis, we explored the influence of the dose of fluticasone furoate-vilanterol (100/25 mg vs 200/25 mg once daily). Subgroups were compared using the residual c2 test from the Peto odds ratios

3. Ergebnisdarstellung

Qualitätsbewertung: the studies had a high methodologic quality

Ergebnisse:

Characteristics of the Included Studies

Study	Duration, ek	Patients, No. (% female)	Mean age (range), y	Racial characteristics	Mean baseline FEV_1, % predicted	Primary outcome	Selected comparisons
Bateman et al[24]	24–78	2019 (67)	42 (≥12)	W, 74%; A, 11%; AA, 5%	68	Asthma exacerbations	Fluticasone furoate–vilanterol, 100/25 μg once daily, vs fluticasone furoate, 100 μg once daily
Bernstein et al[25]	12	1039 (61)	46 (≥12)	W, 88%; A, <1%; AA, <1%	68	Weighted mean FEV_1	Fluticasone furoate–vilanterol, 100/25 μg once daily, vs fluticasone furoate –vilanterol, 200/25 μg once daily, vs fluticasone furoate, 100 μg once daily
Bleecker et al[26]	12	609 (58)	40 (≥12)	W, 84%; A, 8%; AA, <1%	68	Trough FEV_1 and @weighted mean FEV_1	Fluticasone furoate–vilanterol, 100/25 μg once daily, vs fluticasone furoate, 100 μg once daily
Busse et al[27]	52	503 (63)	38 (≥12)	W, 67%; A, 25%; AA, 7%	74	AEs, SAEs Asthma exacerbations	Fluticasone furoate–vilanterol, 100/25 μg once daily, vs fluticasone furoate –vilanterol, 200/25 μg once daily, vs fluticasone propionate, 500 μg twice daily
Lin et al[28]	12	309 (59)	48 (≥12)		63	PM PEF	Fluticasone furoate–vilanterol, 200/25 μg once daily, vs fluticasone propionate, 500 μg twice daily
O'Byrne et al[29]	24	586 (59)	46 (≥12)	W, 84%; A, 9%; AA, 7%	67	Trough FEV_1 and weighted mean FEV_1	Fluticasone furoate–vilanterol, 200/25 μg once daily, vs fluticasone furoate, 200 μg once daily, vs fluticasone propionate, 500 μg twice daily
Woodcock et al[30]	24	806 (61)	43 (≥12)	W, 59%; A, 31%; AA, 10%	64	Weighted mean FEV_1	Fluticasone furoate–vilanterol, 100/25 μg once daily, vs fluticasone propionate –salmeterol, 250/50 μg twice daily

Abbreviations: A, Asian; AA, African American; AE, adverse event; ICS, inhaled corticosteroids; FEV_1, forced expiratory volume in 1 second; PEF, peak expiratory flow; SAE, serious adverse event; W, white.

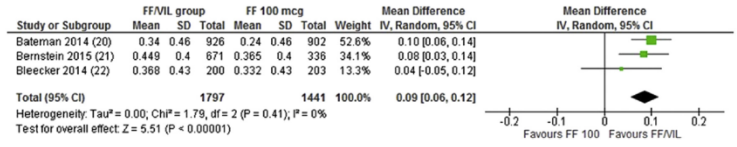


Figure 2. Pooled mean differences for trough forced expiratory volume in 1 second at the end of treatment (change from baseline) with 95% confidence intervals of eligible studies comparing fluticasone furoate–vilanterol and fluticasone furoate, 100 μg.

Fluticasone furoate-vilanterol vs. fluticasone furoate, 100 mg (3 Studien) (no statistical heterogeneity among studies)

- fluticasone furoate-vilanterol significantly increased the percentage of patients symptom free and reduced the use of rescue medication.

Fluticasone furoate-vilanterol also reduced significantly the number of patients with at least 1 severe asthma exacerbation (9.1% vs 13.2%, NNTB ¼ 24).

- no statistical significant differences in the rate of AEs, SAEs, pneumonia, or cardiac events (1.4% vs 1.3%) among both groups

Fluticasone Furoate-Vilanterol Group vs Fluticasone Propionate, 500 mg (3 Studien[27-29])

- mean change from baseline in weighted FEV1 significantly increased by 140 mL at the end of treatment (fluticasone furoate-vilanterol)
- fluticasone furoate-vilanterol group presented significantly increases in morning and evening PEF (32.6 and 25.7 L/min, respectively)
- fluticasone furoate-vilanterol significantly increased the percentage of patients symptom free and reduced the number of patients with at least 1 severe asthma exacerbation (1.3% vs 2.4%, NNTB ¼ 88).
- No statistical difference in health status. Safety outcomes revealed no significant differences in AEs (1.4% vs 2.4%) or in the occurrence of pneumonia (0.4% vs 0.2%)
- fluticasone furoate-vilanterol group had a nonsignificant small increase in the frequency of cardiac events (6.4% vs 1.8%) compared with fluticasone propionate (Ergebnis von einer Studie[27])

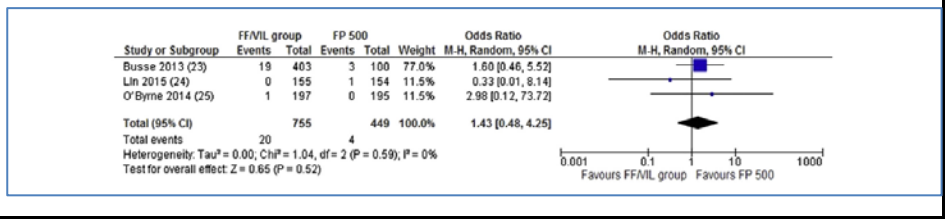
Fluticasone FuroateeVilanterol, 100/25 mg, vs Fluticasone FuroateeVilanterol, 200/25 mg (2 Studien[25,27])

- overall incidence of withdrawals, severe asthma exacerbations, AEs, SAEs, or pneumonia was similar across both fluticasone furoate-vilanterol doses.
- On the basis of data available in 1 study[25] there were nonsignificant differences in terms of pulmonary function (FEV1, and PEF) and symptoms. Finally, also according to data from 1 study[27] the increase of the fluticasone furoate dose was associated with a rise of cardiac events (2.0% to 7.4%).

Fluticasone FuroateeVilanterol, 100/25 mg, vs Fluticasone PropionateeSalmeterol, 250/50 mg (1 Studie[30])

- At 24 weeks, there were no differences in trough FEV1, asthma control, health status, and safety across both treatment groups.

Pooled odds ratios for the rate of cardiac events on treatment with 95% confidence intervals of eligible studies comparing fluticasone furoateevilanterol group and fluticasone propionate, 500 mg.



	4. Anmerkungen/Fazit der Autoren In conclusion, according to the data from this systematic review, the use of once-daily fixed fluticasone furoate-vilanterol combination revealed a slight increase in terms of lung function compared with ICS monotherapy (fluticasone furoate and fluticasone propionate). However, the significance of advantages in other outcomes was unclear. The lack of therapeutic advantage and a trend toward an increased risk of cardiac events do not support the use of fluticasone furoateevilanterol, 200/25 mg, and require close and careful monitoring. Future studies should focus on comparison of fluticasone furoateevilanterol and other combination therapies for safety and efficacy in larger and racially diverse cohorts and studies conducted for a longer duration. 5. Hinweise durch FB Med In den Studien sind Patienten ab 12 Jahren eingeschlossen
Velayati A et al., 2015 [38]. Comparison of the effectiveness and safety of formoterol versus salmeterol in the treatment of patients with asthma: A systematic review and meta-analysis	1. Fragestellung This study is conducted to evaluate the safety and effectiveness of **formoterol versus salmeterol** in the treatment of patients with asthma
	2. Methodik Population: adult asthmatic patients Intervention/ Komparator: formoterol vs. salmeterol Endpunkt: k.A. Suchzeitraum (Aktualität der Recherche): 07/2012 (Search was updated on 02/2013) Anzahl eingeschlossene Studien/Patienten (Gesamt): 12 RCTs (n=1661) Qualitätsbewertung der Studien: Cochrane Risk of Bias & Jaded Scale Heterogenität: Statistical heterogeneity was measured by the I^2 test
	3. Ergebnisdarstellung Charakteristik der eingeschlossenen Studien (inkl. Qualitätsbewertung)

First author	Year	Country	Study setting and time period	Sample	Dosage of salmeterol	Dosage of formoterol	Outcome	Quality score
Rutten-van	1998	UK, Switzerland Sweden, France, Spain, Italy	RCT 6 months	482	50 µg Twice a day	12 µg Twice a day	EFDs Quality of life	2
John J. Condemi	2001	USA	RCT 6 months	528	50 µg Twice a day	12 µg Twice a day	EFDs PEF	2
Julia A. Nightingale	2002	UK	RCT 4 months	528	50 µg Twice a day	12 µg Twice a day	PEF FEV1	4
Klaus F. Rabe	1993	Germany	RCT 1-day	12	50 µg 100 µg Once a day	12 µg 24 µg Once a day	FEV1	2
Campbell	1999	UK	RCT 8 weeks	469	50 µg Twice a day	12 µg Twice a day	PEF	2
Palmqvist	1997	Sweden	RCT 12 h	28	50 µg NA	6 µg 12 µg 24 µg NA	FEV1	4
H. J van der Woude	2001	Netherland	RCT 2 weeks	19	100 µg Twice a day	24 µg Twice a day	FEV1 Borg score	5
Hanneke J. van der Woude	2004	Netherland	RCT 4 days	21	50 µg Twice a day	12 µg Twice a day	FEV1 Borg score	4
Rosa D. Grembiale	2002	Italy	RCT 3 days	10	50 µg Twice a day	12 µg Twice a day	FEV1	2
Alison Grove	1996	UK	RCT 12 h	10	50 µg NA	12 µg NA	FEV1	1
Brian J. Lipworth	1998	Scotland	RCT 10 days	10	50 µg Twice a day	12 µg Twice a day	FEV1	1
Valentine Lemaigre	2006	Belgium	RCT NA	30	NA	NA	FEV1	2

NA =Not available; RCT = Randomized clinical trials; FEV1 = Forced expiratory volume in 1 s; PEF = Peak expiratory flow; EFDs = Episode-free days

mean forced expiratory volume 1 s, 12 h after inhalation of the drug (3 Studien) Palmqvist et al.,[23] Grembiale et al.,[24] and Rabe et al.[25]

- These studies were homogeneous, and meta-analysis was performed ($\chi = 0.14$, $P = 0.93$, $I = 0\%$).
- mean difference was −0.02 (−0.22, 0.18); there is no statistical difference between formoterol 12 µg and salmeterol 50 µg in mean FEV1 at 12 h after inhalation of medication.
- According to the JADAD score of studies with this outcome, this lack of difference appears to be valid in the mean FEV1.

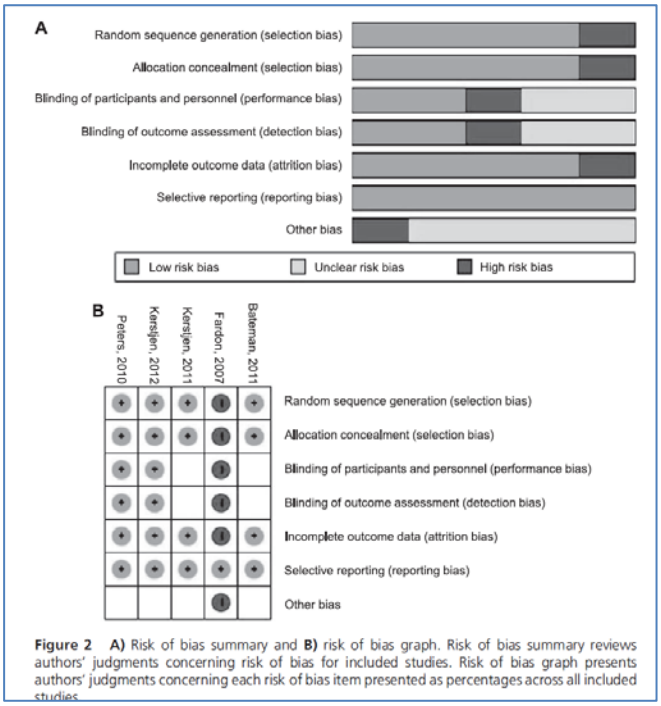
forced expiratory volume 1 s after inhalation of methacholine (2 Studien) van der Woude et al.[26,27]

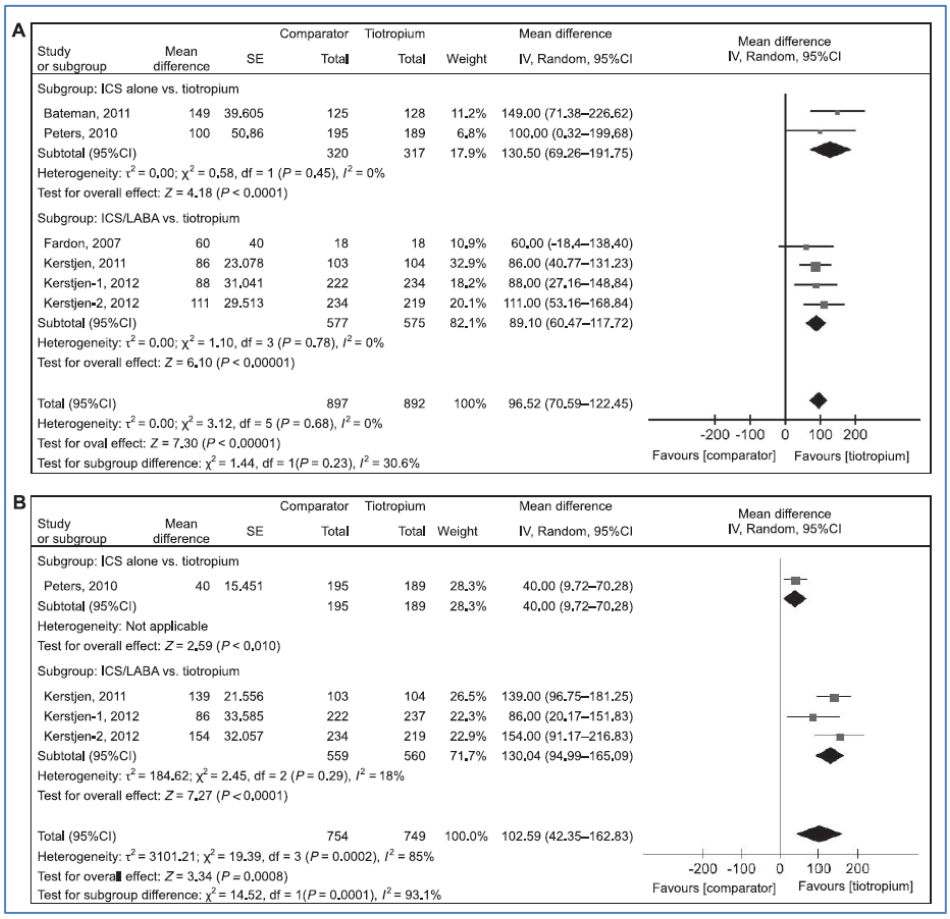
- According to the meta-analysis results, this is a significant difference as 5.23 (1.11-9.34). Therefore, the use of salmeterol 50 µg after inhalation of methacholine reduced more the FEV1 than that of formoterol 12 µg; in these two studies, the ratio dosage of formoterol to salmeterol is same and these studies are similar in this regard, so this point has been considered as restitution of this analysis, and these results should be taken with caution.
- van der Woude study was sponsored by AstraZeneca Company but in another study did not mention the conflict of interest.

number of days without an attack (2 Studien) Rutten-van Mölken et al.[28] and Condemi[29]

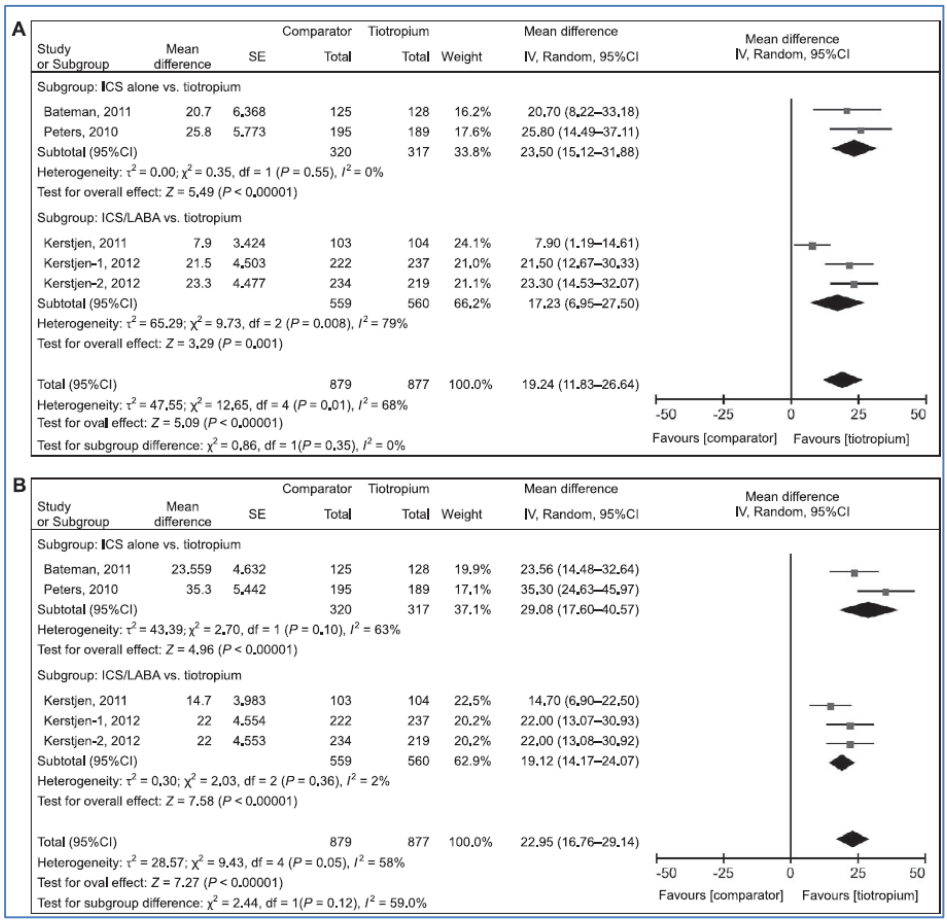
- These studies were homogeneous, and meta-analysis was performed ($\chi = 0.00$, $P = 0.96$, $I = 0\%$).
- According to the meta-analysis results, mean difference was 1.71 (0.19, 3.22); this difference is statistically significant, and therefore, the number of days without an attack after use of salmeterol 50 µg is more

	than that of formoterol 12 µg. • studies were sponsored by Novartis Company → a review of the quality evaluation of these two articles indicates a medium quality. **<u>Borg score after inhalation of drugs (2 Studien)</u>** van der Woude et al.[26,27] • These studies were homogeneous, and meta-analysis was performed (χ =0.05, P = 0.82, I = 0%). Forest plot of these studies is shown in Figure 5. • According to the meta-analysis results, this difference is not statistically significant as 0.06 (−1.95, 2.06) and, therefore, there is no difference in the score after inhalation of 50 µg salmeterol and 12 µg formoterol, in these two studies, the ratio dosage of formoterol to salmeterol is same and two studies are similar in this regard, so this point has been considered as restitution of this analysis, and these results should be taken with caution. van der Woude study was sponsored by AstraZeneca Company but in another study did not mention the conflict of interest.
	4. Anmerkungen/Fazit der Autoren The data from included studies shows that, more efficacy has been achieved with Salmeterol, especially in some outcomes such as the percent decrease in FEV1 after inhalation of Methacholine, and the number of days without an attack; and therefore, the administration of Salmeterol seems to be beneficial for patients, compared with Formoterol. 5. Hinweise durch FB Med The weaknesses of this study include lack of access to some databases such as EMBASE
Lee SW et al., 2014 [27]. Long-acting anticholinergic agents in patients with uncontrolled asthma: a systematic review and meta-analysis	1. Fragestellung We performed a systematic review and meta-analysis of tiotropium in asthma treatment. We assessed whether this drug can improve pulmonary function, quality of life and acute exacerbation in asthma patients and thus function to control this disease.
	2. Methodik <u>Population:</u> adults aged ≥18 years (poorly controlled asthma despite ICS or ICS + LABA use) <u>Intervention:</u> tiotropium <u>Komparator:</u> placebo or a double dose of ICSs <u>Endpunkte:</u> changes in trough/peak forced expiratory volume in 1 s (FEV1) and forced volume capacity (FVC); quality of life; change in asthma-free days; frequency of rescue medicine use; Asthma Control

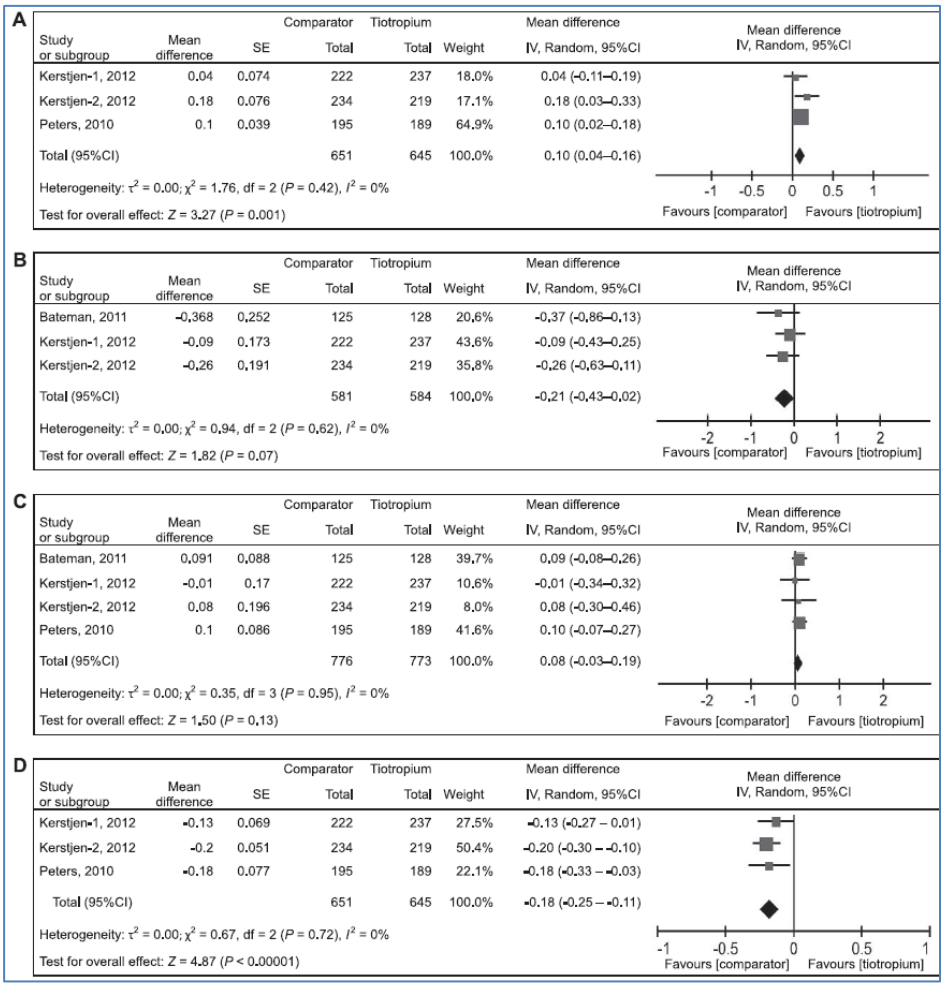
	Questionnaire (ACQ) score; number of severe acute exacerbations during follow-up; and frequency of serious adverse events Suchzeitraum (Aktualität der Recherche): Juni 2013 Anzahl eingeschlossene Studien/Patienten (Gesamt): Six trials from five studies were thus included in the final analysis and a total of 1635 asthma patients (tiotropium vs. control: 894 vs. 899) Qualitätsbewertung der Studien: Cochrane risk of bias tool Heterogenität: Heterogeneity was assessed using I^2
	3. Ergebnisdarstellung Qualitätsbewertung:  **Figure 2** **A)** Risk of bias summary and **B)** risk of bias graph. Risk of bias summary reviews authors' judgments concerning risk of bias for included studies. Risk of bias graph presents authors' judgments concerning each risk of bias item presented as percentages across all included studies Ergebnisse: **The differences of A) trough and B) peak forced expiratory volume in 1 second (ml) for tiotropium vs. comparators. Comparators include placebo or double dose of ICS.**



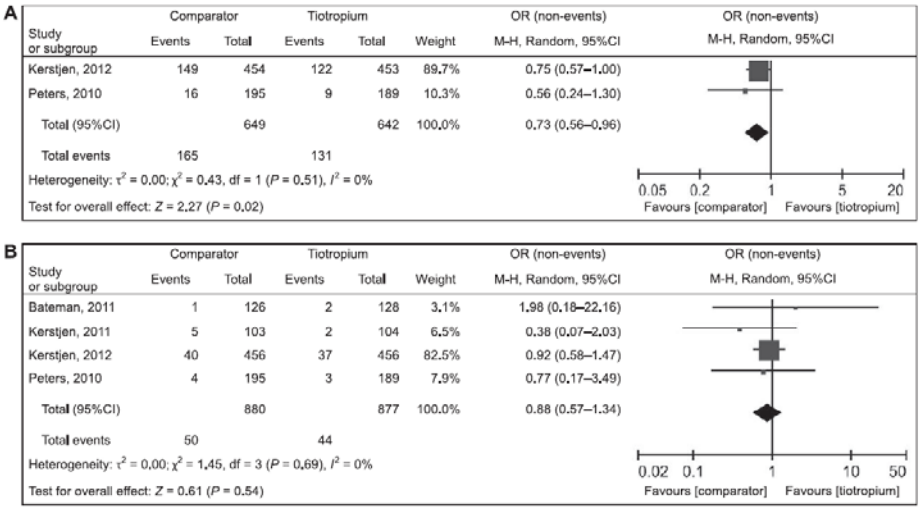
The differences of A) morning and B) evening peak expiratory flow rate (l/min) for tiotropium vs. comparators. Comparators include placebo or double dose of ICS.



Changes in A) AQLQ, B) the number of days with rescue medicine use, C) change in asthma-free days and D) changes in ACQ. Comparators include placebo or double dose of ICS.



Changes in A) severe acute exacerbation and B) serious adverse events. Comparators include placebo or double dose of ICS.



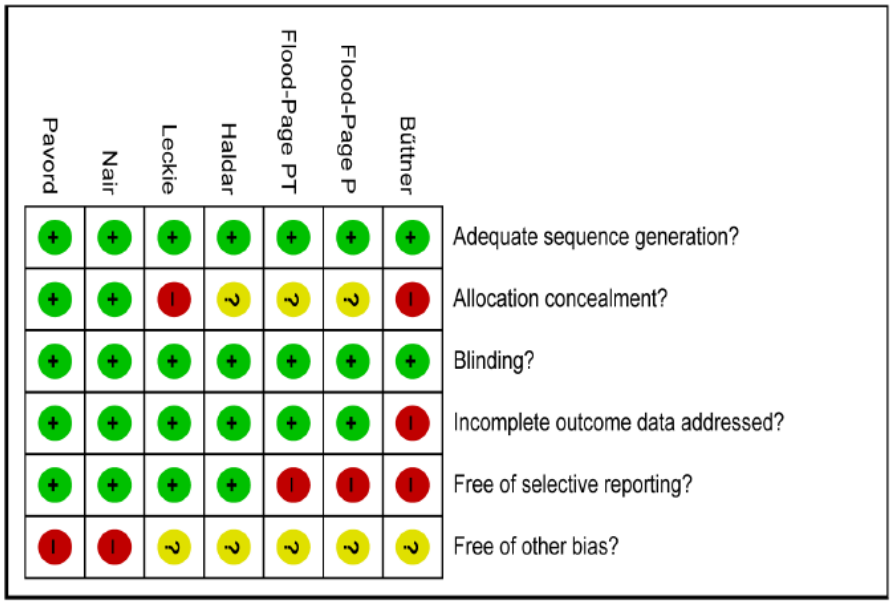
4. Anmerkungen/Fazit der Autoren

Our study results show that tiotropium, an LAMA, can improve pulmonary function and quality of life and reduce the number of severe exacerbations without increasing severe adverse events in short-term follow-up (648 weeks) in relatively young patients (mean age range 42.2–54.8) with uncontrolled asthma despite ICS or ICS-LABA use.

	Tiotropium also showed a tendency to increase the number of asthma-free days and reduce rescue medication use, although this was not statistically significant.
Rodrigo GJ et al., 2015 [35]. What Is the Role of Tiotropium in Asthma? A Systematic Review With Meta-analysis	1. Fragestellung The aim of this systematic review was to assess the efficacy and safety of tiotropium in patients with asthma.
	2. Methodik Population: adults and adolescents aged >12 years with symptomatic stable asthma of any severity and receiving inhaled corticosteroids (ICSs) or an ICS plus long-acting b 2 -agonist (LABA) Intervention: tiotropium Komparator: any treatment Endpunkte: (1) primäre Endpunkte: FEV 1 and morning and evening peak expiratory flow (PEF) (2) sekundäre Endpunkte: rescue medication use (puffs/d), asthma symptom-free days per week, quality of life (Mini-Asthma Quality of Life Questionnaire [AQLQ] total score), 10 asthma control (Asthma Control Questionnaire 7 [ACQ-7] total score), 11 ACQ-7 responder rate determined by the percentage of patients with an improvement (decrease) in the ACQ-7 total score of at least 0.5 points, asthma exacerbations (number of patients with one or more episodes that required the use of systemic corticosteroids), withdrawals (total and due to AEs), and safety (AEs and serious adverse events [SAEs]) as secondary outcomes Suchzeitraum (Aktualität der Recherche): September 2014 Anzahl eingeschlossene Studien/Patienten (Gesamt): 13 RCTs (n=4966) Qualitätsbewertung der Studien: Cochrane Risk of bias tool Heterogenität: I^2 test (≤25%, absent; 26%-39%, unimportant; 40%-60%, moderate; 60%-100%, substantial).
	3. Ergebnisdarstellung Qualitätsbewertung: All but one of the studies showed a low risk of bias in the six items of the Cochrane instrument; the one study 4 had an unclear sequence generation, and concealment was judged to have a high risk of bias. Ergebnisse: **(1) Tiotropium as Add-on to ICS (10 Studien)** • Tiotropium OD as add-on to ICS was associated with significant improvements in morning and evening PEF (mean change from

	baseline, 22-24 L/min, P, .00001) compared with ICS monotherapy. The results were statistically homogeneous, and there was no evidence of systematic bias (P 5 .74 and P 5 .73). • In the same way, tiotropium improved peak FEV 1 (mean change from baseline, 150 mL; P, .00001) and trough FEV 1 (mean change from baseline, 140 mL; P, .00001) compared with ICS alone. Both comparisons were statistically homogeneous • tiotropium significantly improved AQLQ and ACQ-7 total scores from baseline (0.07 [P, .03] and 2 0.14 units [P, .00001], respectively), although these improvements and their CIs did not achieve the MCID. • tiotropium showed a greater likelihood of achieving an MCID in ACQ-7 (66.3% vs 60.2%), with an NNTB of 16. • tiotropium produced a significant decrease in the number of patients with at least one episode of asthma exacerbation compared with ICS monotherapy (10.5% vs 13.3%), with an NNTB of 36. • no significant differences in asthma symptom-free days, total withdrawals, withdrawals due to AEs, AEs (34.6% vs 34.6%), and SAEs (1.9% vs 2.1%). **(2) Tiotropium Plus ICS vs LABA Plus ICS (4 Studien)** • Tiotropium significantly improved morning PEF more than, although the magnitude of the increase was small (6.6 L/min). • no significant difference in evening PEF between groups • no significant differences in peak and trough FEV 1 • On the contrary, patients receiving LABA experienced a significant reduction in the use of rescue medication (-0.2 puffs/d) and an improved AQLQ total score (0.12 units) but without reaching the MCID. • no significant differences in asthma symptom-free days; ACQ-7 total score and responder rate; number of patients with at least one asthma exacerbation; and withdrawals, AEs (67.6% vs 72.8%), and SAEs (1.9% vs 2.5%). **(3) Tiotropium as Add-on to LABA Plus ICS (3 Studien)** • Tiotropium as add-on to LABA plus ICS was associated with signifi cant improvements in morning and evening PEF (16 [P, .0004] and 20 L/min [P, .00001], respectively) → heterogeneity among studies was moderate, and there was no evidence of systematic bias (P 5 .15 and P 5 .68). I • triple therapy increased peak and trough FEV 1 significantly by a magnitude of 120 and 80 mL, respectively, compared with LABA plus ICS • combination of tiotropium, LABA, and ICS resulted in significant increases in AQLQ and ACQ-7 total scores, they did not reach the MCDI. • tiotropium showed a greater likelihood of achieving an MCID in ACQ-7 score (58.1% vs 45.1%), with an NNTB of 8. • Triple therapy showed a significant reduction in the number of patients

	who experienced at least one asthma exacerbation (18.2% vs 24.0%), with an NNTB of 17. no significant differences between groups in the remainder of outcomes.
	4. Anmerkungen/Fazit der Autoren Tiotropium resulted noninferiorly to salmeterol and superiorly to placebo in patients with moderate to severe asthma who were not adequately controlled by ICS or ICS/ salmeterol. Major benefits were concentrated in the increase in lung function and in the case of patients with severe asthma, in the reduction of exacerbations. In conclusion, this systematic review suggests that tiotropium is noninferior to salmeterol and superior to placebo in patients with moderate to severe asthma Major benefits are concentrated in lung function and, in patients with severe asthma, an increase in control and a decrease in exacerbations. Thus, tiotropium might be an alternative to LABA in patients with mild to moderate asthma whose symptoms are not well controlled by ICS alone or as an add-on therapy in patients with severe asthma not controlled with available medications, including ICS plus LABA. 5. Hinweise durch FB Med Patientenpopulation umfasst u.a. Studien mit Patienten ab 12 Jahren
Liu Y et al., 2013 [28]. Efficacy of Anti-Interleukin-5 Therapy with Mepolizumab in Patients with Asthma: A Meta-Analysis of Randomized Placebo-Controlled Trials	1. Fragestellung To provide an overview of the relevant studies, and to evaluate the efficacy of administering mepolizumab on blood and sputum eosinophils, lung function, clinical exacerbations, asthma control, and asthma related quality of life in patients with varied types of asthma.
	2. Methodik <u>Population:</u> patients with asthma <u>Intervention:</u> mepolizumab <u>Komparator:</u> keine Angaben <u>Endpunkt:</u> eosinophil counts in blood or sputum and clinical outcomes <u>Suchzeitraum (Aktualität der Recherche):</u> search in PubMed, Embase, ISI Web of Science, Cochrane CENTRAL, and Scopus for articles published until January 2013 <u>Anzahl eingeschlossene Studien/Patienten (Gesamt):</u> 7 RCTs davon sind für das AWG 3 RCTs relevant (Nair 2009, Haldar 2009, Pavord 2012) <u>Qualitätsbewertung der Studien:</u> Jadad score (randomization, blinding, concealment of allocation, reporting of withdrawals, and generation of

	random numbers) und eigene Skala: (1) adequate sequence generation; (2) allocation concealment; (3) blinding; (4) incomplete outcome data addressed; (5) free of selective reporting; and (6) free of other bias zur Klassifikation in low/medium/high risk of bias Publikationsbias untersucht: Funnel plot, Beggs Test: no publication bias was detected
	3. Ergebnisdarstellung Im AWG 3 RCTs relevant: Nair 2009, Haldar 2009, Pavord 2012 (siehe auch Powell C et al., 2015 [34] Cochrane Review) Relevanten Studien (Nair 2009, Haldar 2009, Pavord 2012): low risk of bias: Jadad Score: 4-5 Punkte (siehe Anhang, Abb. 3: Studiencharakteristika)  **Wirksamkeit und Lebensqualität (alle Vergleiche Mepolizomab vs. Placebo)** *blood eosinophils (mean difference)* • Nair 2009: -0,56 (-0,90; -0.22) • Haldar 2009: n.s. • Pavord 2012: -0.71 (-1.02; -0.39) *Sputum esoinophils:* • Nair 2009: n.s. • Haldar 2009: -5.86 (-9.32; -2.40) *FEV1 (mean difference)* • Nair 2009: n.s. • Pavord 2012: n.s. *Exazerbation (OR und 95% CI)*

- Nair 2009: OR=0,20 (0.01-4,75)
- Haldar 2009: OR=0,41 (0,12-1,42)
- Pavord 2012: OR=0,16 (0.09-0,26)

Juniper Asthma Control Questionnaire (JACQ

- Nair 2009/Pavord 2012: n.s.
- Overall effect: n.s.

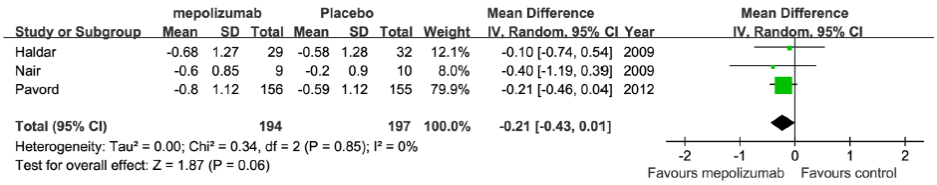


Figure 9. The effects of mepolizumab on Juniper Asthma Control Questionnaire (JACQ).

Asthma Quality of Life Questionnaire (AQLQ).

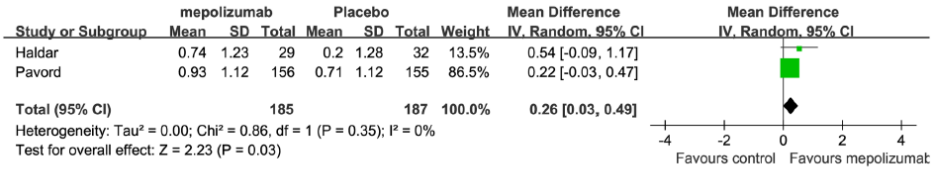


Figure 10. The effects of mepolizumab on Asthma Quality of Life Questionnaire (AQLQ).

Subgruppenanalyse zu eosinophilem Asthma:

Table 2. Subgroup analyses for the effect of mepolizumab on blood eosinophil counts and asthma exac

Variables	Blood eosinophil counts			Asthma exacerbation	
	No.of studies	OR (95% CI)	*P* for Subgroup difference	No.of studies	OR (95% CI)
Subgroup analysis					
No. of subjects			0.25		
<100	5	−0.20 (−0.37, −0.03)		2	0.37 (0.12,0.98)
≥100	2	−0.46 (−0.88, −0.04)		2	0.28 (0.08,0.98)
Types of asthma			0.0008		
Eosinophilic asthma	3	−0.62 (−0.84, −0.39)		3	0.18 (0.11, 0.29)
Mild or moderate asthma	4	−0.18 (−0.30, −0.06)		1	0.56 (0.25, 1.22)

4. Anmerkungen/Fazit der Autoren

Mepolizumab treatment appears to be useful for control of exacerbations and improve asthma-related quality of life in individuals with persistent airway eosinophilia, but may not associate with significant improvement in functional airways outcomes. The results highlight the importance of selection the subgroup of patients with asthma might derive clinical benefit from mepolizumab treatment

Lai T et al., 2015 [26].

Long-term efficacy and safety of omalizumab

1. Fragestellung

Currently, limited information is available to clinicians regarding the long-term efficacy of omalizumab treatment for allergic asthma. In this report, we aimed to (i) systematically review the evidence regarding the long-term efficacy of omalizumab in patients with persistent uncontrolled allergic asthma, and to (ii) discuss the cost-effectiveness evidence published for

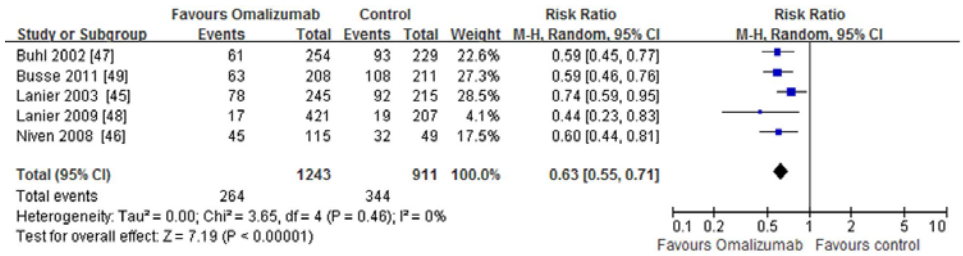
in patients with persistent uncontrolled allergic asthma: a systematic review and meta-analysis *Sowie* **Lai T et al., 2015 [25].** Corrigendum: Long-term efficacyand safety of omalizumab in patients with persistent uncontrolled allergic asthma: a systematic review and metaanalysis	omalizumab in this patient population.
	2. Methodik Population: patients with persistent, uncontrolled, moderate-to severe allergic asthma in spite of high-dose ICS or ICS plus LABA Intervention: Omalizumab, mindestens 52 Wochen Komparator: k.A. Endpunkt: k.A. Suchzeitraum (Aktualität der Recherche): k.A. Anzahl eingeschlossene Studien/Patienten (Gesamt): 6 (2749) Qualitätsbewertung der Studien: k.A.
	3. Ergebnisdarstellung The overall designs of these studies were as follows: after a run-in phase (4–8 weeks), omalizumab was administrated as an adjunctive therapy to inhaled or oral corticosteroids for 16 to 28 weeks (stable steroid phase), followed by a steroid-reduction phase of 12 to 28 additional weeks, during which doses were decreased only if patients met strict criteria for steroid reduction. We double-counted two end points (stable steroid phase and steroid-reduction phase), and using these single primary efficacy endpoints (end of the steroid-reduction phase), included the rates of clinically significant asthma exacerbations, reductions in ICS doses, Global Evaluation of Treatment Effectiveness (GETE), Asthma Quality of Life Questionnaire (AQLQ), asthma symptom scores, lung function, and adverse events (AEs), over a period of 52 weeks. Table 2 | Risk of bias of the included studies Study / Sequence generation / Allocation concealment / Data collection blinded / Complete outcome data / Selective outcome reporting Finn et al[44] / No / Yes / Yes / Yes / Yes Lanier et al[45] / No / Yes / Yes / Yes / Yes Niven et al[46] / Yes / No / Yes / Yes / Yes Buhl et al[47] / No / Yes / Yes / Yes / Yes Lanier et al[48] / Yes / Yes / Yes / Yes / Yes Busse et al[49] / No / Yes / Yes / Yes / Yes

Table 1 | Characteristic of randomized controlled trials included

Source	Study design	Female/Patients (No.)	Age (y)‡	IgE (IU/ml)‡	Severity/FEV_1 (%pred)‡	Study duration (weeks)	Exacerbation definition
Finn 2003[44]	**DB**				**S**	**52**	
Omalizumab		164/268	39.3	172.5	68.2		A worsening of asthma symptoms and was severe enough to require treatment with oral or intravenous corticosteroids or a doubling of the subject's baseline inhaled BDP dose.
Control		146/257	39.0	186.3	67.7		
Lanier 2003[45]	**DB**				**S**	**52**	
Omalizumab		150/245	68.8	173.4	68.8		Worsening of asthma requiring treatment with oral or intravenous corticosteroids or doubling of the patient's most recent BDP maintenance dose.
Control		119/215	68.2	186.2	68.2		
Niven 2008[46]	**OL**				**S**	**52**	
Omalizumab		86/115	38.7	NA	65.6		Asthma worsening requiring treatment with systemic corticosteroids and the ADRIs, unscheduled physician visit, or hospitalization/emergency room visit.
Control		34/49	39.3	NA	64.1		
Buhl 2002[47]	**DB**				**M-S**	**52**	
Omalizumab		124/254	41	220.2	70.0		Worsening of asthma requiring treatment with oral or parenteral corticosteroids or doubling of the patient's most recent BDP maintenance dose.
Control		120/299	40	204.1	70.4		
Lanier 2009[48]	**DB**				**M-S**	**52**	
Omalizumab		134/421	8.7	476.0	86.0		Worsening of asthma symptoms requiring doubling of baseline ICS dose and/or treatment with rescue systemic corticosteroids for 3 days.
Control		69/207	8.4	456.9	87.2		
Busse 2011[49]	**DB**				**M-S**	**60**	
Omalizumab		86/208	10.9	NA	92.9		A need for systemic glucocorticoids, hospitalization, or both, in accordance with a recent report by the American Thoracic Society/European Respiratory Society[5].
Control		91/211	10.8	NA	92.2		

‡The data are shown as mean.
FEV_1, forced expiratory volume in one second; DB, Double-blind; OL, Open-label; M, moderate; S, severe; BDP, beclomethasone dipropionate; ADRIs, annual rate of asthma deterioration-related incidents; NA, not available.
[5]Reddel HK, *et al.* An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med* **180**, 59–99 (2009).

Exazerbationen



During the steroid-reduction phase, ICS doses were significantly decreased in omalizumab-treated patients compared with the placebo group (RR 1.86, 95% CI [1.51, 2.29]; p <, 0.0001).
Heterogeneity was not observed (I^2 5 0%, p = 0.47).

At 52 weeks, both GETE (an excellent or good response) and AQLQ scores (≥1.5 points from baseline) favored omalizumab (RR1.54, 95%CI [1.38, 1.72]; p < 0.00001 and RR 2.08, 95% CI [1.03, 4.20]; p = 0.04 respectively) (table 3).

Symptoms and FEV/ PEF

With regard to asthma symptoms and lung function, descriptive analysis

methods were utilized, as most of these data were unavailable or unsuitable for analysis. Two RCTs demonstrated greater reductions in asthma symptom scores than placebo46,48. However, the effects of omalizumab on lung function were discrepant.
Only one RCT demonstrated that pulmonary function (FEV1) was significantly better in the omalizumab group than in the control group.

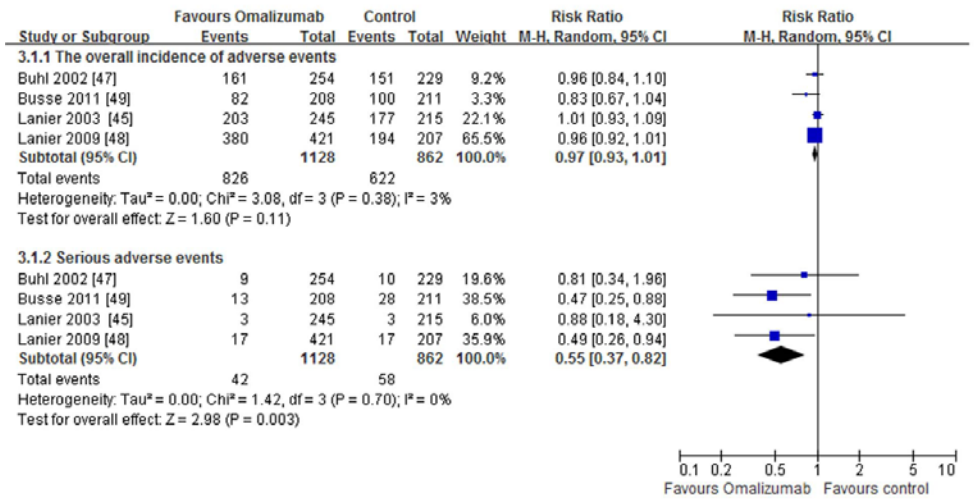
Supplemental table 2. Analysis of other outcomes (Omalizumab vs control)

Outcome measure	Omalizumab effect	No. (O/C)	O (Δ)	C (Δ)	Difference between groups: *P* value	Comments
Asthma symptom score						
	Niven 2008 [46] ↑↑	115/49	NA	NA	$p < 0.05$	At 1 year, asthma score was significantly improved in the omalizumab group compared with control.
	Liner 2009 [48] ↑↑	421/207	NA	NA	$p < 0.01$	Nocturnal asthma symptom score, -0.63 [0.72] vs -0.50 [0.71].
Pulmonary function						
Lanier 2003 [45]		245/215				
	FEV_1, L ↔		NA	NA	$P = 0.16$	The corresponding between-group differences in FEV_1 at weeks 52 were 52 ml.
Niven 2008 [46]		115/49				
	FEV_1, L ↑↑		Δ = + 0.19	NA	$P < 0.05$	Throughout the 1-year treatment period representing a between-group difference of 320 ml.
Buhl 2002 [47]						
	FEV_1, %predicted ↔	254/299	NA	NA	NA	No statistically significant differences in FEV_1 were seen between the treatment groups at any time point during the extension.
Busse 2011 [49]						
	FEV_1, %predicted ↔	208/211	NA	NA	$p = 0.30$	No statistically significant differences in FEV_1 were seen between two groups during follow-up.

↑↑ Omalizumab better than (with statistical significance); ↑ Omalizumab better than control (without statistical significance); ↔ Omalizumab comparable with control. O, Omalizumab; C, Control; Δ, The mean change from baseline; NA, not available; FEV_1, forced expiratory volume in 1 second.

AE

Four studies assessed adverse events (AEs), and omalizumab was well tolerated. Common adverse events included the following: lower respiratory tract infection, nasopharyngitis, headache, injection site pain, injection site reaction and arthralgia. Based on the results of the meta-analysis, the numbers of patients reporting AEs was similar in both treatment groups (RR 0.97, 95% CI [0.93, 1.01]; p = 0.11). Statistical heterogeneity was not observed (I^2 5 3%, p = 0.38). Serious adverse events, such as death, asthma exacerbation, pruritus, acute appendicitis, sphenoid sinusitis, intestinal obstruction, and mild chest pain were reported. However, none of these was considered drug-related. The incidence and profile of serious adverse events were slightly lower in the omalizumab group (RR 0.55, 95% CI [0.37, 0.82]; p= 0.003). Statistical heterogeneity was not observed (I^2=0%, p=0.70) . No clinically relevant abnormalities in laboratory tests (including platelet count) were observed.



Gesamtauswertungen und Subgruppen

Table 3 | Results of subgroup and sensitivity analyses from a meta-analyses of randomized controlled trials

Trials	Asthma exacerbation[44–49]	Withdrew ICS completely[45,47]	Change in GFTE score[44,48,49]	AQLQ ≥ 1.5[44,46]	Adverse events[45,47–49]
	← RR (95%CI), P value →				
All trials[44–49]	0.63 [0.55, 0.71] <0.0001	1.86 [1.51, 2.29] <0.0001	1.54 [1.38, 1.72] <0.00001	2.08 [1.03, 4.20] =0.04	0.97 [0.93, 1.01] =0.11
Subgroup analyses					
Risk of bias					
Low[46,48]	0.57 [0.43, 0.74] <0.0001	–	1.42 [1.24, 1.62] <0.00001	3.23 [1.58, 6.59] =0.001	0.96 [0.92, 1.01] =0.12
High[44,45,47,49]	0.64 [0.55, 0.75] <0.00001	1.86 [1.51, 2.29] <0.0001	1.65 [1.45, 1.87] <0.00001	1.57 [1.23, 2.01] =0.0003	0.96 [0.88, 1.06] =0.44
Age of patients					
Adolescents and adults[44–47]	0.65 [0.56, 0.76] <0.00001	1.86 [1.51, 2.29] <0.0001	1.60 [1.30, 1.97] <0.00001	2.08 [1.03, 4.20] =0.04	0.99 [0.93, 1.07] =0.54
Children[48,49]	0.41 [0.29, 0.58] <0.00001	–	1.53 [1.30, 1.80] <0.00001	–	0.91 [0.75, 1.12] =0.06
Asthma severity					
Moderate-sever[44–46]	0.68 [0.55, 0.84] =0.0004	2.37 [1.17, 4.78] =0.02	1.60 [1.30, 1.97] <0.00001	2.08 [1.03, 4.20] =0.04	1.01 [0.93, 1.09] =0.88
Severe[47–49]	0.58 [0.49, 0.69] <0.00001	1.82 [1.46, 2.26] <0.0001	1.53 [1.30, 1.80] <0.00001	–	0.95 [0.89, 1.02] =0.28
Intervention					
Omalizumab/ ICS[44,45,47,48]	0.63 [0.50, 0.80] =0.0002	1.86 [1.51, 2.29] <0.0001	1.49 [1.33, 1.66] <0.00001	1.57 [1.23, 2.01] =0.0003	0.98 [0.93, 1.02] =0.32
Omalizumab/ICS + LABA[46,49]	0.59 [0.49, 0.72] <0.00001	–	1.68 [1.43, 1.97] <0.00001	3.23 [1.58, 6.59] =0.001	0.83 [0.67, 1.04] =0.10
Sensitivity analyses					
Open label[46]	0.60 [0.44, 0.81] =0.001	–	–	3.23 [1.58, 6.59] =0.001	–
Double-blinded[44,45,47–49]	0.63 [0.54, 0.73] <0.0001	1.86 [1.51, 2.29] <0.0001	1.54 [1.38, 1.72] <0.00001	1.57 [1.23, 2.01] =0.0003	0.97 [0.93, 1.01] =0.11
Fixed-effects model[44–49]	0.62 [0.55, 0.71] <0.00001	1.88 [1.52, 2.33] <0.0001	1.52 [1.37, 1.68] <0.00001	1.77 [1.40, 2.24] <0.00001	0.96 [0.91, 1.01] =0.08

RR, relative risk; CI, confidence interval; ICS, included inhaled corticosteroid; GETE, Global Evaluation of Treatment Effectiveness; AQLQ, Asthma Quality of Life Questionnaire; LABA, long-acting beta2-agonists.

4. Anmerkungen/Fazit der Autoren

Omalizumab was associated with significant improvements in quality of life and the Global Evaluation of Treatment Effectiveness. Omalizumab also allowed patients to completely withdraw from inhaled corticosteroid therapy and did not increase the overall incidence of adverse events.

However, there was insufficient evidence that omalizumab reduced the incidence of exacerbations, and the cost-effectiveness of omalizumab varied across studies. Our data indicated that omalizumab use for at least 52 weeks in patients with persistent uncontrolled allergic asthma was accompanied by an acceptable safety profile, but it lacked effect on the asthma exacerbations.

Leitlinien

Global Initiative for Asthma (GINA), 2017 [17]. Global strategy for asthma management and prevention; updated 2017	*GINA – Global Initiative for Asthma*
	Methodik <u>Grundlage der Leitlinie:</u> • LL-Committee: members are recognized leaders in asthma research and clinical practice with the scientific expertise • Jährliches Update der LL • Vor jedem Treffen des LL-Committee: PubMed search is performed for the previous year using filters established by the Committee • After initial screening by the Program Director and Chair of the Science Committee, each publication identified by the above search is reviewed for relevance and quality by members of the Science Committee. Each publication is allocated to at least two Committee members, but all members receive a copy of all of the abstracts and have the opportunity to provide comments • During Committee meetings, each publication that was assessed by at least one member to potentially impact on the GINA report is discussed. Decisions to modify the report or its references are made by consensus by the full Committee, or, if necessary, by an open vote of the full Committee • The Committee makes recommendations for therapies that have been approved for asthma by at least one regulatory agency, but decisions are based on the best available peer-reviewed evidence and not on labeling directives from government regulators • GINA conducts an ongoing twice-yearly update of the evidence base for its recommendations. • Levels of evidence are assigned to management recommendations where appropriate. **LITERATURE REVIEWED FOR GINA 2017 UPDATE** The GINA report has been updated in 2017 following the routine twice-yearly review of the literature by the GINA Science Committee. The literature searches for 'clinical trial' publication types (see above) and meta-analyses identified a total of 304 publications, of which 190 were screened out for relevance and/or quality. The remaining 114 publications were reviewed by at least two members of the Science Committee, and 66 were subsequently discussed at a face-to-face meeting (37 'clinical trials' and 29 meta-analyses). A list of key changes in GINA 2017 can be found on p.10, and a tracked changes copy of the 2016 report is archived on the GINA website. <u>LoE :</u> Abbildung

Evidence level	Sources of evidence	Definition
A	Randomized controlled trials (RCTs) and meta-analyses. Rich body of data.	Evidence is from endpoints of well designed RCTs or meta-analyses that provide a consistent pattern of findings in the population for which the recommendation is made. Category A requires substantial numbers of studies involving substantial numbers of participants.
B	Randomized controlled trials (RCTs) and meta-analyses. Limited body of data.	Evidence is from endpoints of intervention studies that include only a limited number of patients, post hoc or subgroup analysis of RCTs or meta-analysis of such RCTs. In general, Category B pertains when few randomized trials exist, they are small in size, they were under-taken in a population that differs from the target population of the recommendation, or the results are somewhat inconsistent.
C	Nonrandomized trials. Observational studies.	Evidence is from outcomes of uncontrolled or non-randomized trials or from observational studies.
D	Panel consensus judgment.	This category is used only in cases where the provision of some guidance was deemed valuable but the clinical literature addressing the subject was insufficient to justify placement in one of the other categories. The Panel Consensus is based on clinical experience or knowledge that does not meet the above listed criteria.

Sonstige methodische Hinweise

Empfehlungen sind mit Primärquellen verknüpft.

keine Angabe des GoR.

Hinweis: Pharmacological treatment → siehe Anhang 1

STEP 4: Two or more controllers plus as-needed reliever medication

→ Preferred option (adults/adolescents): combination low dose ICS/formoterol as maintenance and reliever treatment, OR combination medium dose ICS/LABA plus as-needed SABA

The selection of Step 4 treatment depends on the prior selection at Step 3. Before stepping up, check for common problems such as incorrect inhaler technique, poor adherence, and environmental exposures, and confirm that the symptoms are due to asthma (Box 2-4, p22).

For adult and adolescent patients with ≥1 exacerbations in the previous year, combination low dose ICS/formoterol as maintenance and reliever treatment is more effective in reducing exacerbations than the same dose of maintenance ICS/LABA or higher doses of ICS **(Evidence A).** This regimen can be prescribed with low dose budesonide/formoterol or beclometasone/formoterol as in Step 3; the maintenance dose may be increased if necessary. For patients taking low dose maintenance ICS/LABA with as-needed SABA, whose asthma is not adequately controlled, treatment may be increased to medium dose ICS/LABA **(Evidence B);** combination ICS/LABA medications are as for Step 3.

Other options:

Tiotropium (long-acting muscarinic antagonist) by mist inhaler may be used as add-on therapy for adult or adolescent patients with a history of exacerbations (**Evidence A**); it is not indicated in children <12 years.

Combination high-dose ICS/LABA may be considered in adults and adolescents, but the increase in ICS dose generally provides little additional benefit **(Evidence A),** and there is an increased risk of side-effects. A high dose is recommended only on a trial basis for 3–6 months when good asthma control cannot be achieved with medium dose ICS plus LABA and/or a third controller (e.g. LTRA or sustained-release theophylline **(Evidence B).** Theophylline should not be used in children.

For medium or high dose budesonide, efficacy may be improved with dosing four times daily **(Evidence B),** but adherence may be an issue. For other ICS, twice-daily dosing is appropriate **(Evidence D).** Other options for adults or adolescents that can be added to a medium- or high-dose ICS but that are less efficacious than adding LABA, include LTRA **(Evidence A**), or low dose sustained-release theophylline **(Evidence B).**

STEP 5: Higher level care and/or add-on treatment

→ Preferred option: referral for specialist investigation and consideration of add-on treatment

Patients with persistent symptoms or exacerbations despite correct inhaler technique and good adherence with Step 4 treatment and in whom other controller options have been considered**,** should be referred to a specialist with expertise in management of severe asthma **(Evidence D)**

Treatment options that may be considered at Step 5 (if not already tried) are described in Box 3-14 (p.70). They include:

- Add-on tiotropium (long-acting muscarinic antagonist) in patients aged ≥12 years with a history of exacerbations despite Step 4 treatment. Add-on tiotropium by mist inhaler improves lung function and increases the time to severe exacerbation (Evidence B).[189]
- Add-on anti-immunoglobulin E (anti-IgE) (omalizumab) treatment: for patients aged ≥6 years with moderate or severe allergic asthma that is uncontrolled on Step 4 treatment[199,200] (Evidence A).
- Add-on anti-interleukin-5 treatment (subcutaneous mepolizumab, intravenous reslizumab): for patients aged ≥12 years with severe eosinophilic asthma that is uncontrolled on Step 4 treatment (Evidence B).[201-203]
- Sputum-guided treatment: for patients with persisting symptoms and/or exacerbations despite high-dose ICS or ICS/LABA, treatment may be adjusted based on eosinophilia (>3%) in induced sputum. In severe asthma, this strategy leads to reduced exacerbations and/or lower doses of ICS[147] (Evidence A).
- Add-on treatment with bronchial thermoplasty: may be considered for some adult patients with severe asthma [126] (Evidence B). Evidence is limited and in selected patients (see p.51 and Appendix Chapter 6). The long term effects compared with control patients, including for lung function, are not known.
- Add-on low dose oral corticosteroids (≤7.5 mg/day prednisone equivalent): may be effective for some adults with severe asthma[126] (Evidence D); but are often associated with substantial side effects[204,205] (Evidence B). They should only be considered for adults with poor symptom control and/or frequent exacerbations despite good inhaler technique and adherence with Step 4 treatment, and after exclusion of other contributory factors. Patients should be counseled about potential side-effects (Evidence D).[205] They should be assessed and monitored for risk of corticosteroid-induced osteoporosis, and those expected to be treated for ≥3 months should be provided with relevant lifestyle counselling and prescription of therapy for prevention of osteoporosis (where appropriate).[206]

Stepping up asthma treatment

- Asthma is a variable condition, and periodic treatment adjustments by the clinician and/or the patient may be needed.
- *Sustained step up (for at least 2–3 months)*: some patients may fail to respond adequately to initial treatment. A step up in treatment may be recommended (Box 3-5, p31) if the symptoms are confirmed to be due to asthma; inhaler technique and adherence are satisfactory; and modifiable risk factors such as smoking have been addressed (Box 3-8, p38). Any step-up should be regarded as a therapeutic trial, and the response reviewed after 2–3 months. If there is no response, treatment should be reduced to the previous level, and alternative treatment options or referral considered.
- *Short-term step up (for 1–2 weeks)*: an occasional short-term increase in maintenance ICS dose for 1–2 weeks may be necessary; for example, during viral infections or seasonal allergen exposure. This may be initiated by the patient according to their written asthma action plan (Box 4-2, p61), or by the health care provider.

Day-to-day adjustment: for patients prescribed combination budesonide/formoterol or beclometasone/formoterol as maintenance and

	reliever treatment, the patient adjusts the number of as-needed doses of ICS/formoterol from day to day according to their symptoms, while continuing the maintenance dosage.
SIGN, 2016 [37]. British guideline on the management of asthma	SIGN = Scottish Intercollegiate Guidelines Network in Kooperation mit British Thoracic Society
	Methodik <u>Grundlage der Leitlinie:</u> This guideline was issued in 2014 and sections of the guideline will be updated on a biennial basis. The evidence base for this guideline was synthesised in accordance with SIGN methodology. A systematic review of the literature was carried out using an explicit search strategy devised by a SIGN Evidence and Information Scientist. Databases searched include Medline, Embase, Cinahl, PsycINFO and the Cochrane Library. Internet searches were carried out on various websites including the US National Guidelines Clearinghouse. The main searches were supplemented by material identified by individual members of the development group. Each of the selected papers was evaluated by two members of the group using standard SIGN methodological checklists before conclusions were considered as evidence. <u>Update</u>: Between 2004 and 2012 sections within the guideline were updated annually. Subsequently, updating moved to a biennial basis, beginning with the 2014 update. This edition of the guideline was issued in 2016. All updates were made available on both the BTS (www.brit-thoracic.org.uk) and SIGN (www.sign.ac.uk) websites. Any updates to the guideline in the period between scheduled updates will be noted on the SIGN and BTS websites. ➔ The 2016 version includes a complete revision of the section on diagnosis, a major update to the section on pharmacological management of asthma, and updates to the sections on supported self-management, non-pharmacological management of asthma, acute asthma, difficult asthma, occupational asthma, and organisation and delivery of care. Loe/GoE:

KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS	
LEVELS OF EVIDENCE	
1^{++}	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1^{+}	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1^{-}	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2^{++}	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2^{+}	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2^{-}	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion
GRADES OF RECOMMENDATION	
Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.	
A	At least one meta-analysis, systematic review, or RCT rated as 1^{++}, and directly applicable to the target population; *or* A body of evidence consisting principally of studies rated as 1^{+}, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2^{++}, directly applicable to the target population, and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 1^{++} or 1^{+}
C	A body of evidence including studies rated as 2^{+}, directly applicable to the target population and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 2^{++}
D	Evidence level 3 or 4; *or* Extrapolated evidence from studies rated as 2^{+}
GOOD PRACTICE POINTS	
✓	Recommended best practice based on the clinical experience of the guideline development group

Empfehlungen sind mit Literaturquellen versehen.

Hinweis: Pharmacological treatment → siehe Anhang 2

MAINTENANCE AND RELIEVER THERAPY

A **In adults over the age of 18, combined maintenance and reliever therapy can be considered for patients who have a history of asthma attacks on medium dose ICS or ICS/LABA**

ADDITIONAL ADD-ON THERAPIES

If there is no improvement when a LABA is added, stop the LABA and try:

- an increased dose of ICS
- an LTRA
- a LAMA (LAMA are not licensed for this indication)

Increased dose of ICS

If there is a response to LABA, but control remains suboptimal, continue with the LABA and increase the dose of ICS to medium (adults) or low dose (children 5–12 years).[456] >12 years

If, as occasionally happens, there is no response to inhaled long-acting β_2 agonist, stop the LABA and increase the dose of ICS to medium (adults) or low dose (children) if not already on this dose.[456] 4

D D **If asthma control remains suboptimal after the addition of an inhaled long-acting β_2 agonist then the dose of inhaled corticosteroids should be increased from low dose to medium dose in adults or from very low dose to low dose in children** (5–12 years), **if not already on these doses.**

An LTRA

Evidence to support the use of leukotriene receptor antagonists (LTRA) as an add-on therapy to ICS plus LABA is lacking and evidence for their use is largely based on extrapolation from trials of LTRA as add-on therapy to ICS alone. The addition of LTRA to ICS may provide improvement in lung function, a decrease in asthma attacks, and an improvement in symptoms in adults and children over five years of age, although reported benefits differ between studies and evidence is limited in children.[435,464,465] — >12 years, 1++

A systematic review of studies comparing the addition of LTRA to ICS with the addition of LABA to ICS showed that the addition of LABA to ICS was more effective at reducing asthma attacks (the primary outcome) and improving secondary outcomes including SABA use, symptoms and quality of life in adults, although differences were generally small. There was insufficient evidence on which to base conclusions regarding which add-on therapy is more effective in children.[453] — 1++

In adults, the addition of LTRA to ICS is superior to ICS alone and has a similar effect on asthma control to high-dose ICS. High-dose ICS, however, appears superior to ICS-LTRA for some pulmonary function indices, although further studies to investigate this are required.[466] — 1+

A LAMA

A review of RCTs in adults taking tiotropium bromide, a long-acting muscarinic antagonist (LAMA), in addition to ICS plus LABA compared with ICS plus LABA, reported fewer asthma exacerbations (although results were inconclusive), improved lung function and some benefits relating to asthma control in those taking tiotropium, but no improvement in quality of life. Evidence relating to serious adverse effects was inconclusive but fewer non-serious adverse events were reported in those taking tiotropium. In two of the three trials included in the review patients were taking high-dose ICS, although it was not possible to draw conclusions about the effect of tiotropium in those taking different doses of ICS plus LABA.[467] — >12 years, 1++

There is insufficient evidence to suggest that addition of tiotropium to ICS in patients inadequately controlled on ICS alone has any benefit over addition of LABA to ICS.[468] The addition of LABA to ICS remains the first choice for add-on treatment in adults. In adults with asthma who do not respond to ICS plus LABA, the addition of tiotropium to ICS is a possible, although 'off-label' alternative.[469 470] — >12 years, 1++, 1+

A review comparing the addition of tiotropium to ICS with increased dose of ICS in adults found only one study suitable for inclusion and insufficient evidence to say whether adding tiotropium to ICS ('off-label' use) is safer or more effective than increasing the dose of ICS.[471] — 1+

OTHER APPROACHES

Theophyllines may improve lung function and symptoms, but side effects occur more commonly.[444] — >12 years, 1+

Slow-release β_2 agonist tablets may also improve lung function and symptoms, but side effects occur more commonly.[443] — 1++

Addition of short-acting anticholinergics is generally of no value.[445,472] Addition of nedocromil is of marginal benefit.[438,446] — 1+

✓ If control remains inadequate after stopping a LABA and increasing the dose of inhaled corticosteroid, consider sequential trials of add-on therapy, ie leukotriene receptor antagonists, theophyllines, slow-release β_2 agonist tablets (in adults only)

HIGH-DOSE THERAPIES

In a small proportion of patients asthma is not adequately controlled on a combination of short-acting β_2 agonist as required, medium-dose ICS, and an additional drug, usually a LABA. There are very few clinical trials in this specific patient group to guide management.

In adults, the addition of tiotropium to high-dose ICS plus LABA may confer some additional benefit although results are currently inconclusive *(see section 7.4.3)*. Further research is needed to confirm possible benefits or harms of tiotropium in combination with different doses of ICS/LABA.[467] The following recommendations are largely based on extrapolation from trials of add-on therapy to ICS alone *(see section 7.4)*.

>12 years

1++

D D

If control remains inadequate on medium dose (adults) **or low dose** (children) **of an inhaled corticosteroid plus a long-acting β_2 agonist, the following interventions can be considered:**

- **increase the inhaled corticosteroids to high dose** (adults) **or medium dose** (children 5-12 years)* ***or***
- **add a leukotriene receptor antagonist** ***or***
- **add a theophylline** ***or***
- **add slow-release β_2 agonist tablets, although caution needs to be used in patients already on long-acting β_2 agonists,** ***or***
- **add tiotropium** (adults).

There are no controlled trials indicating which of these is the best option, although the potential for side effects is greater with theophyllines and β_2 agonist tablets.

✓ If a trial of an add-on treatment is ineffective, stop the drug (or in the case of increased dose of inhaled corticosteroid, reduce to the original dose).

✓ Before proceeding to continuous or frequent use of oral steroid therapy, refer patients with inadequately controlled asthma, especially children, to specialist care.

✓ Although there are no controlled trials, children (all ages) who are under specialist care may benefit from a trial of higher dose ICS (greater than 800 micrograms/day) before moving to use of oral steroids.

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

NICE, 2017 [29]. Mepolizumab for treating severe refractory eosinophilic asthma *Siehe auch:* **CADTH, 2016 [5].** Mepolizumab (NucalaGlaxoSmithKline Inc.) Indication: severe eosinophilic asthma **NIHR Horizon Scanning Centre, 2014 [31].** Mepolizumab for severe refractory eosinophilic asthma – first line	• Recommendations • • 1.1 Mepolizumab, as an add-on to optimised standard therapy, is recommended as an option for treating severe refractory eosinophilic asthma in adults, only if: • the blood eosinophil count is 300 cells/microlitre or more in the previous 12 months and • the person has agreed to and followed the optimised standard treatment plan and - has had 4 or more asthma exacerbations needing systemic corticosteroids in the previous 12 months or - has had continuous oral corticosteroids of at least the equivalent of prednisolone 5 mg per day over the previous 6 months and • the company provides the drug with the discount agreed in the patient access scheme. • • 1.2 At 12 months of treatment: • stop mepolizumab if the asthma has not responded adequately or • continue treatment if the asthma has responded adequately and assess response each year. • An adequate response is defined as: • at least 50% fewer asthma exacerbations needing systemic corticosteroids in those people with 4 or more exacerbations in the previous 12 months or • a clinically significant reduction in continuous oral corticosteroid use while maintaining or improving asthma control. • *1.3* This guidance is not intended to affect the position of patients whose treatment with mepolizumab was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop. • • Evidence for clinical effectiveness • Evidence for mepolizumab compared with placebo came from 3 randomised controlled trials. • Evidence for mepolizumab compared with omalizumab came from a network meta-analysis. The trials included different patient populations, including differences in disease severity.The committee concluded that the comparison was not clinically relevant or methodologically robust and therefore did not consider this comparison further.
NICE, 2017 [30]. Reslizumab for treating	• Recommendations • 1.1 Reslizumab, as an add-on therapy, is recommended as an option for the treatment of severe eosinophilic asthma

severe eosinophilic asthma *Siehe auch:* **CADTH, 2017 [6].** Reslizumab (Cinqair) **NIHR Horizon Scanning Centre, 2015 [32].** Reslizumab for eosinophilic asthma	that is inadequately controlled in adults despite maintenance therapy with high-dose inhaled corticosteroids plus another drug, only if: • the blood eosinophil count has been recorded as 400 cells per microlitre or more • the person has had 3 or more severe asthma exacerbations needing systemic corticosteroids in the past 12 months and • the company provides reslizumab with the discount agreed in the patient access scheme. • • 1.2 At 12 months: • stop reslizumab if the asthma has not responded adequately or • continue reslizumab if the asthma has responded adequately and assess response each year. • • An adequate response is defined as: • a clinically meaningful reduction in the number of severe exacerbations needing systemic corticosteroids or • a clinically significant reduction in continuous oral corticosteroid use while maintaining or improving asthma control. • • 1.3 These recommendations are not intended to affect treatment with reslizumab that was started in the NHS before this guidance was published. Adults having treatment outside these recommendations may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop. • • Availability, nature and quality of evidence: • The committee noted that there is limited data on the effectiveness of reslizumab in people who are on maintenance corticosteroids, because only 19% and 12% of people respectively in study 3082 and study 3083 fulfilled this criterion. The committee concluded that treatment with reslizumab may be considered for people who are not taking maintenance oral corticosteroids, but that it would be most beneficial for people who have multiple exacerbations despite maintenance oral corticosteroid use. •

Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) am 24.01.2018

#	Suchfrage
1	MeSH descriptor: [Asthma] explode all trees
2	asthma*:ti (Word variations have been searched)
3	#1 or #2
4	#3 Publication Year from 2013 to 2018, in Cochrane Reviews (Reviews only) and Technology Assessments

SR, HTAs in Medline (PubMed) am 24.01.2018

#	Suchfrage
1	"asthma/therapy"[MeSH Terms] OR "asthma/drug therapy"[MeSH Terms]
2	asthma*[Title]
3	(#2) AND ((((((((((treatment*[Title/Abstract]) OR therapy[Title/Abstract]) OR therapies[Title/Abstract]) OR therapeutic[Title/Abstract]) OR monotherap*[Title/Abstract]) OR polytherap*[Title/Abstract]) OR pharmacotherap*[Title/Abstract]) OR effect*[Title/Abstract]) OR efficacy[Title/Abstract]) OR treating[Title/Abstract]) OR treated[Title/Abstract]) OR management[Title/Abstract]) OR drug*[Title/Abstract]
4	#1 OR #3
5	(#4) AND ((Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]) OR (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))))
6	(#5) AND ("2013/01/01"[PDAT] : "3000"[PDAT])
7	(#6) NOT "The Cochrane database of systematic reviews"[Journal]
8	(#7) NOT retracted publication[ptyp]

Leitlinien in Medline (PubMed) am 24.01.2018

#	Suchfrage
1	asthma[MeSH Major Topic]
2	asthma*[Title]
3	#1 OR #2
4	(#3) AND ((Guideline[ptyp] OR Practice Guideline[ptyp] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp]) OR ((guideline*[Title] OR recommendation*[Title]) NOT (letter[ptyp] OR comment[ptyp] OR medline[sb])))
5	(#4) AND ("2013/01/01"[PDAT] : "3000"[PDAT])

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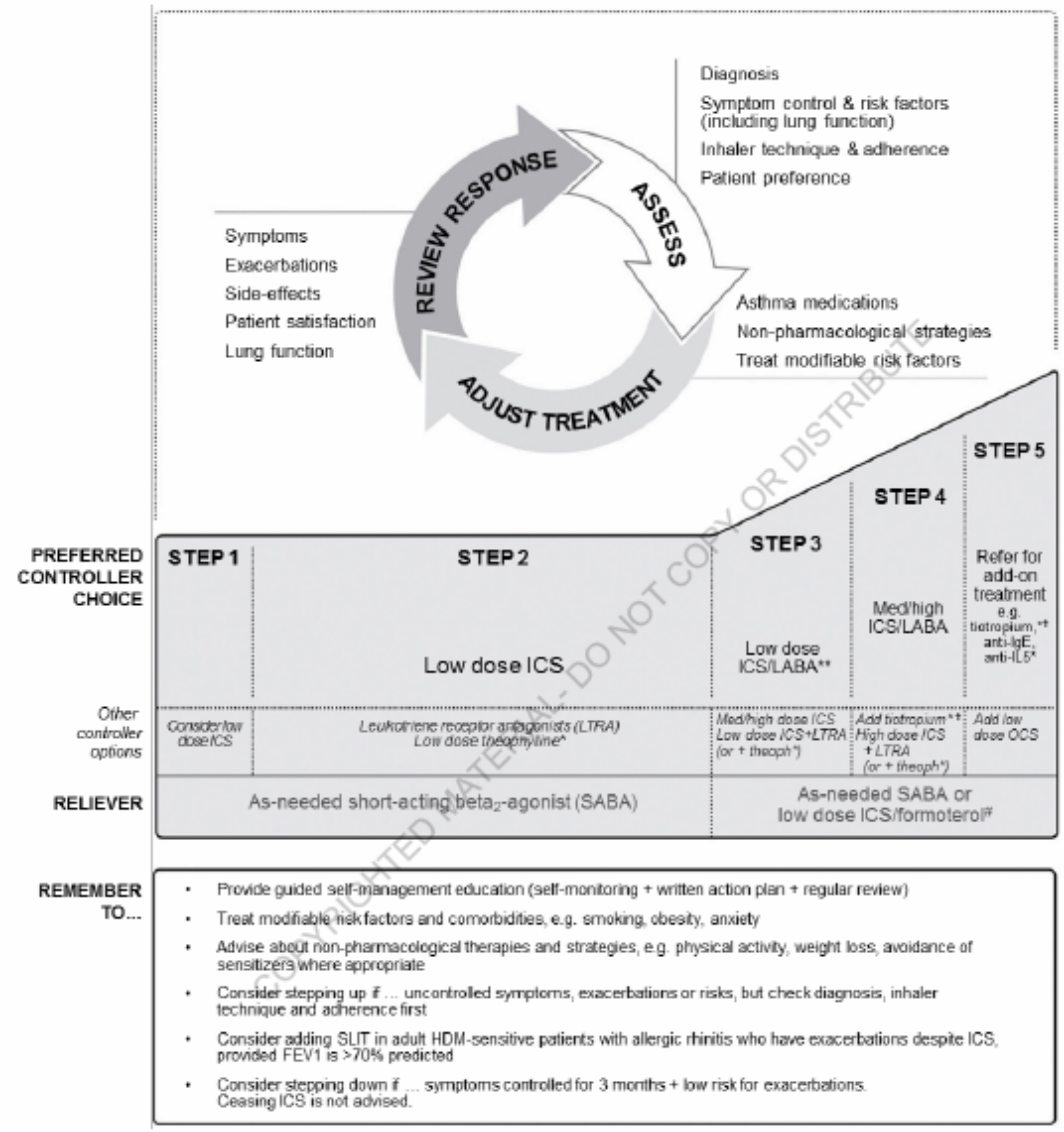
Anhang

Global Initiative for Asthma (GINA), 2017 [17]: Global strategy for asthma management and prevention; updated 2017

Box 3-5. Stepwise approach to control symptoms and minimize future risk



ICS: inhaled corticosteroids; LABA: long-acting beta$_2$-agonist; med: medium dose; OCS: oral corticosteroids; SLIT: sublingual immunotherapy. See Box 3-6 (p.44) for low, medium and high doses of ICS for adults, adolescents and children 6–11 years. See Chapter 3 Part D (p.66) for management of exercise-induced bronchoconstriction.

* Not for children <12 years.
** For children 6–11 years, the preferred Step 3 treatment is medium dose ICS.
# Low dose ICS/formoterol is the reliever medication for patients prescribed low dose budesonide/formoterol or low dose beclometasone/formoterol maintenance and reliever therapy.
† Tiotropium by mist inhaler is an add-on treatment for patients with a history of exacerbations; it is not indicated in children <12 years.

SIGN, 2016 [37]. British guideline on the management of asthma (2016)