

# **Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie**

**und**

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

**Vorgang: 2019-B-195-z Mometasonfuorat,  
Indacaterolacetat und Glycopyrroniumbromid**

Stand: August 2019

## I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

### Mometasonfuorat, Indacaterolacetat und Glycopyrroniumbromid zur Behandlung von 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 <i>Übersicht II: Zugelassene Arzneimittel im Anwendungsgebiet:</i>
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	<p>Beschluss des G-BA über eine Änderung der Arzneimittel-Richtlinie (AM-RL):</p> <ul style="list-style-type: none"><li>- Mepolizumab (Anlage XII – Nutzenbewertung nach §35a SGB V, Beschluss vom 21. Juli 2016)</li><li>- Reslizumab (Anlage XII – Nutzenbewertung nach §35a SGB V, Beschluss vom 6. Juli 2017)</li><li>- Benralizumab (Anlage XII – Nutzenbewertung nach §35a SGB V, Beschluss vom 2. August 2018)</li></ul> <p>Beschluss des G-BA über eine Änderung der Arzneimittel-Richtlinie (AM-RL) - Anlage IV: Therapiehinweis zu Omalizumab (Beschluss vom 17. Dezember 2015)</p> <p>DMP-Richtlinie (DMP-RL): Asthma</p>
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	siehe <i>Evidenzsynopse</i>

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Wirkstoff ATC-Code Handelsname	Anwendungsgebiet (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Mometasonfuorat, Indacaterolacetat und Glycopyrroniumbromid ATC-Code Handelsname®	Geplantes Anwendungsgebiet laut Beratungsanforderung: „Erhaltungstherapie des Asthma bei Erwachsenen, deren Asthma nicht adäquat mit mittel-bis hochdosierten inhalativen Kortikosteroiden und langwirksamen Beta-2-Agonisten kontrolliert ist“
<b>Beta-2-Sympathomimetika (inhalativ; kurzwirkend) (SABA)</b>	
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)
<b>Beta-2-Sympathomimetika (systemisch; kurzwirkend) (SABA)</b>	
Reprotorol	Zur kurzfristigen Behandlung des schweren bronchospastischen Anfalls und des Status asthmaticus. (FI Bronchospasmin, Stand 02/2016)

II. Zugelassene Arzneimittel im Anwendungsgebiet	
R03CC14 Bronchospasmin	
<b>Beta-2-Sympathomimetika (inhalativ; langwirkend) (LABA)</b>	
Salmeterol R03AC12 Serevent®	<p>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).</p> <p>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.</p> <p><u>Warnhinweis:</u> Serevent Dosier-Aerosol und Serevent Diskus sollen nicht für die Akutbehandlung eines Asthmaanfalls eingesetzt werden. (FI Serevent ® Dosier-Aerosol, Stand 02/2015)</p>
Formoterol R03AC13 Formoterol CT®	<ul style="list-style-type: none"> <li>- Symptomatische Langzeitbehandlung des chronischen mäßigen bis schweren Asthma bronchiale in Kombination mit einer entzündungshemmenden Dauertherapie (z. B. Kortikosteroide).</li> <li>- [...]</li> </ul> <p>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)</p>
<b>Beta-2-Sympathomimetika (oral; kurz-, langwirkend)</b>	
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	Verhütung und Behandlung von Atemwegserkrankungen bei Erwachsenen und Kindern ab 2 Monaten, die mit einer Verengung der

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Salubronch®	<p>Atemwege durch Krämpfe der Bronchialmuskulatur einhergehen (obstruktive Atemwegserkrankungen), wie z. B. bei Asthma bronchiale, chronischer Bronchitis und Blählunge (Lungenemphysem).</p> <p>Hinweis SALBUBRONCH Elixier ist nur für Patienten, die nicht symptomorientiert mit inhalativen <math>\beta_2</math>-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)</p>
Bambuterol R03CC12 Bambec®	<p>Verhütung und Behandlung von Atemwegserkrankungen, die mit einer Verengung der Atemwege durch Krämpfe der Bronchialmuskulatur einhergehen (obstruktive Atemwegserkrankungen).</p> <p>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)</p>
Clenbuterol R03CC13 Spiropent®	<p>Symptomatische Behandlung chronisch obstruktiver Atemwegserkrankungen mit reversibler Atemwegsverengung, wie z. B. Asthma bronchiale oder chronisch obstruktive Bronchitis mit und ohne Emphysem.</p> <p>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)</p>
Clenbuterol/ Ambroxol R03CC63	Akute und chronische Atemwegserkrankungen, die mit spastischen Verengungen, veränderter Sekretbildung und gestörtem Sekrettransport einhergehen, insbesondere spastische Bronchitiden, Emphysembronchitiden

<b>II. Zugelassene Arzneimittel im Anwendungsgebiet</b>	
Spasmo Mucosolvan Saft®	<p>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)</p>
<b>Anticholinergika (inhalativ)</b>	
Tiotropiumbromid R03BB04 Spiriva® Respimat®	<p>[...] Spiriva Respimat ist indiziert als zusätzlicher dauerhaft einzusetzender Bronchodilatator bei Patienten ab 6 Jahren mit schwerem Asthma, die im Vorjahr mindestens eine schwere Exazerbation erfahren haben (siehe Abschnitte 4.2 und 5.1). (FI Spiriva® Respimat®, Stand 10/2018)</p>
<b>Inhalative Corticosteroide (ICS)</b>	
Beclometason R03BA01 Junik®	<p>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)</p>
Budesonid R03BA02 BUDECORT®	<p>Zur Behandlung persistierender Atemwegserkrankungen, wenn die Anwendung von Glukokortikoiden erforderlich ist, wie z.B. bei:  <ul style="list-style-type: none"> <li>- Asthma bronchiale</li> <li>- Chronisch obstruktiver Bronchitis.</li> </ul> (FI Budecort® 200 Novolizer®, Stand 06/2014)</p>
Ciclesonid R03BA08 ALVESCO®	<p>Zur Behandlung von persistierendem Asthma bei Erwachsenen und Jugendlichen (ab 12 Jahren). (FI Alvesco®, Stand 04/2016)</p>
Fluticasone R03BA05	<p>Dauerbehandlung eines persistierenden Asthma bronchiale aller Schweregrade. Hinweis:</p>

II. Zugelassene Arzneimittel im Anwendungsgebiet	
FLUTIDE®	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)
<b>Corticosteroide (systemisch, oral)</b>	
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)
<b>Weitere</b>	
Theophyllin (systemisch) R03DA04 z.B. Theophyllin retard-ratiopharm®	Bronchospasmolytikum/Antiasthmatisches 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 verzögter 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 wird angewendet bei Erwachsenen, Jugendlichen und Kindern (6 bis < 12 Jahre). Die Behandlung mit

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Xolair®	<p>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).</p> <p><b>Erwachsene und Jugendliche (ab 12 Jahren)</b></p> <p>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 &lt; 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.</p> <p>(FI Xolair®, Stand 09/2016)</p>
Mepolizumab R03DX09 Nucala®	Nucala ist angezeigt als Zusatzbehandlung bei schwerem refraktärem eosinophilem Asthma bei Erwachsenen, Jugendlichen und Kindern ab 6 Jahren (siehe Abschnitt 5.1). (FI Nucala , Stand 08/2018)
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)
Benralizumab R03DX10 Fasenra	Fasenra ist angezeigt als Add-on-Erhaltungstherapie bei erwachsenen Patienten mit schwerem eosinophilem Asthma, das trotz hochdosierter inhalativer Kortikosteroide plus lang wirksamer Beta-Agonisten unzureichend kontrolliert ist (siehe Abschnitt 5.1). (FI Fasenra, Stand 02/2019)
Dupilumab D11AH05 Dupixent	Dupixent ist angezeigt als Add-on-Erhaltungstherapie bei Erwachsenen und Jugendlichen ab 12 Jahren mit schwerem Asthma mit Typ-2-Inflammation, gekennzeichnet durch eine erhöhte Anzahl der Eosinophilen im Blut und/oder erhöhtes FeNO (siehe Abschnitt 5.1), das trotz hochdosierter inhalativer Kortikosteroide (ICS) plus einem weiteren zur Erhaltungstherapie angewendeten Arzneimittel unzureichend kontrolliert ist. (FI Dupixent, Stand 05/2019)
<b>Kombinationspräparate (ICS/LABA)</b>	
Beclometason/ Formoterol	Foster ist angezeigt für die regelmäßige Behandlung von Asthma, bei der die Anwendung eines

II. Zugelassene Arzneimittel im Anwendungsgebiet	
R03AK08 Foster®	Kombinationsprodukts (von inhalativem Kortikosteroid und langwirksamem Beta-2-Agonisten) angezeigt ist: <ul style="list-style-type: none"> <li>• Patienten, die mit inhalativen Kortikosteroiden und inhalativen schnellwirksamen Beta-2-Agonisten zur bedarfsweisen Inhalation nicht ausreichend eingestellt sind oder</li> <li>• Patienten, die mit inhalativen Kortikosteroiden und langwirksamen Beta-2-Agonisten in Kombination bereits ausreichend eingestellt sind. (FI Foster, Stand 12/2016)</li> </ul>
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 R03AK11 FLUTIFORM®	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 (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®,

<b>II. Zugelassene Arzneimittel im Anwendungsgebiet</b>	
	Stand 10/2016)
<b>Kombinationspräparate: Anticholinergika/ Beta-2-Sympathomimetikum</b>	
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 nach § 35a SGB**

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## **Abkürzungsverzeichnis**

ACQ	Asthma Control Questionnaire
AE	adverse events
anti-IL-5	anti-interleukin-5
AQLQ	Asthma Quality of Life Questionnaire
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BUD	budesonide
CI	confidence interval
F	formoterol
FEV1	forciertes exspiratorisches Volumen (engl. Forced Expiratory Volume in 1 second)
FP	fluticasone
FVC	Forced vital capacity
GIN	Guidelines International Network
GINA	Global Initiative for Asthma
GoR	Grade of Recommendations
HR	Hazard Ratio
ICS	Inhaled Corticosteroid
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
IV	intravenous
KI	Konfidenzintervall
LABA	long-acting beta <sub>2</sub> -agonists
LAMA	long-acting muscarinic antagonist
LoE	Level of Evidence
NICE	National Institute for Health and Care Excellence
NMA	Netzwerkmetaanalyse
OCS	orales Glucocorticosteroid
OR	Odds Ratio
PEF	Peak expiratory flow
RCTs	randomized controlled trials

RR	Relatives Risiko
SABA	short-acting beta-agonist
SAE	Serious adverse events
SAL	salmeterol
SC	subcutaneous
SIGN	Scottish Intercollegiate Guidelines Network
SiT	single inhaler therapy
TRIP	Turn Research into Practice Database
WHO	World Health Organization

## **1 Indikation**

Erwachsene Patienten, deren Asthma nicht adäquat mit mittel-bis hochdosierten inhalativen Kortikosteroiden und langwirksamen Beta-2-Agonisten kontrolliert ist.

## **2 Systematische Recherche**

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Asthma* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 06.06.2019 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, G-BA, GIN, 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 1311 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 28 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

## **3 Ergebnisse**

### **3.1 G-BA-Beschlüsse/IQWiG-Berichte**

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#### **G-BA, 2018 [12].**

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 21. Juli 2016 / 06. Dezember 2018 – Mepolizumab.

#### **Anwendungsgebiet**

„Nucala® ist angezeigt als Zusatzbehandlung bei schwerem refraktärem eosinophilem Asthma bei erwachsenen Patienten.“

#### **Vergleichstherapie**

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.

#### **Fazit / Ausmaß des Zusatznutzens / Ergebnis**

- 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.

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#### **G-BA, 2017 [11].**

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 6. Juli 2017 / 6. Dezember 2018 – Reslizumab

#### **Anwendungsgebiet**

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.

#### **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.

### **Fazit / Ausmaß des Zusatznutzens / Ergebnis**

- 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, 2018 [10].**

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 02. August 2018 - Benralizumab

#### **Anwendungsgebiet**

Fasenra ist angezeigt als Add-on-Erhaltungstherapie bei erwachsenen Patienten mit schwerem eosinophilem Asthma, das trotz hochdosierter inhalativer Kortikosteroide plus lang wirksamer Beta-Agonisten unzureichend kontrolliert ist.

#### **Vergleichstherapie**

eine patientenindividuelle Therapieeskalation:

- der hochdosierten inhalativen Corticosteroide (ICS) und der langwirksamen Beta-Agonisten (LABA) mit Tiotropium und ggf. orale Corticosteroide (OCS)<sup>a</sup> oder
- bei IgE-vermittelter Pathogenese des Asthmas ggf. Omalizumab zusätzlich zu hochdosierten ICS und LABA und ggf. OCS<sup>a</sup> oder
- ggf. der hochdosierten ICS und LABA mit OCS<sup>a,b</sup> oder
- ggf. der hochdosierten ICS und LABA mit Mepolizumab bei Patienten, die nicht anderweitig eskaliert werden können

<sup>a</sup> Orale Corticosteroide sollten nur kurzzeitig und in der niedrigst-wirksamen Dosis eingesetzt werden. Bei der Behandlung des Asthmas mit OCS ist darauf zu achten, dass die Dosierung von OCS die Cushing-Schwelle möglichst nicht dauerhaft überschreitet. Eine Behandlung von Exazerbationen ist davon abzugrenzen.

<sup>b</sup> Eine Therapie mit OCS ist im Vergleich zu den anderen genannten Wirkstoffen - sofern diese geeignet sind - nicht als zu präferierende Therapieoption anzusehen.

## **Fazit / Ausmaß des Zusatznutzens / Ergebnis**

- a) Erwachsene Patienten mit schwerem eosinophilem Asthma, das trotz hochdosierter inhalativer Corticosteroide plus lang wirksamer Beta-Agonisten unzureichend kontrolliert ist und für die weiteren Möglichkeiten der Therapieeskalation noch nicht ausgeschöpft sind:  
Ein Zusatznutzen ist nicht belegt.
- b) Erwachsene Patienten mit schwerem eosinophilem Asthma, das trotz hochdosierter inhalativer Corticosteroide plus lang wirksamer Beta-Agonisten unzureichend kontrolliert ist und für die weiteren Möglichkeiten der Therapieeskalation bereits ausgeschöpft sind:  
Anhaltspunkt für einen geringen Zusatznutzen.

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## **G-BA, 2019 [8].**

Richtlinie des Gemeinsamen Bundesausschusses zur Zusammenführung der Anforderungen an strukturierte Behandlungsprogramme nach § 137f Absatz 2 SGB V (DMP-Anforderungen-Richtlinie/DMP-A-RL) zuletzt geändert am 17. Januar 2019, Inkrafttreten: 01. April 2019

### **Fazit**

#### **1.5.8.1 Dauertherapie bei Erwachsenen**

Vorrangig sollen zur Dauertherapie die folgenden Wirkstoffgruppen verwendet werden:

##### **1. Basistherapie**

- inhalative Glukokortikosteroide,

2. als Erweiterung dieser Basistherapie kommen zusätzlich zur Gabe von inhalativen Glukokortikosteroiden in Betracht:

- inhalative lang wirksame Beta-2-Sympathomimetika
- Wenn trotz dieser erweiterten Basistherapie ein unkontrolliertes Asthma bronchiale besteht, stehen zur Modifikation bzw. Eskalation zur Verfügung: - langwirksame Anticholinergika
- systemische Glukokortikosteroide
- Leukotrien-Rezeptor-Antagonisten
- Theophyllin (Darreichungsform mit verzögter Wirkstofffreisetzung)
- Antikörper

Bei Patientinnen und Patienten mit trotz Ausschöpfung einer erweiterten Basistherapie nicht ausreichend kontrollierbarem schwerem persistierendem Asthma bronchiale kann eine Behandlung mit Antikörpern (z. B. Anti-IgE-Antikörper oder Anti-IL-5-Antikörper) erwogen werden. Hierfür soll eine Überweisung zum qualifizierten Facharzt oder zur qualifizierten Fachärztin oder zur qualifizierten Einrichtung erfolgen.

Bei Undurchführbarkeit einer Therapie mit inhalativen Glukokortikosterooiden (z. B. Ablehnung oder Unverträglichkeit) als Basismedikation ist vor Verordnung einer unterlegenen alternativen antientzündlichen Therapie ein Aufklärungsgespräch über Risiken dieser Therapieoptionen zu führen.

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## **G-BA, 2019 [9].**

Anlage IV zum Abschnitt H der Arzneimittel-Richtlinie Verordnungseinschränkungen und - ausschlüsse in der Arzneimittelversorgung Therapiehinweise gemäß § 92 Abs. 2 Satz 7 SGB V i. V. m. § 17 AM-RL zur wirtschaftlichen Verordnungsweise von Arzneimitteln.

### **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  $\geq 76$  und  $\leq 1500$  I.E./ml vor Beginn der Behandlung,
- häufige dokumentierte Symptome während des Tages oder nächtliches Erwachen,
- trotz täglicher Therapie mit hochdosierten inhalativen Kortikosteroiden (entsprechend  $> 1000 \mu\text{g}$  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  $\geq 20$  kg und  $\leq 150$  kg.
- Nichtraucher



## 3.2 Cochrane Reviews

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**Farne HA et al., 2017 [7].**

Anti-IL5 therapies for asthma.

### **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.

### **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

#### Endpunkte:

- 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 or more of the outcomes listed here in the trial was not an inclusion criterion for the review.

#### Recherche/Suchzeitraum:

- The search was first conducted in 11/2013 and was updated in 11/2014 and 03/2017

#### Qualitätsbewertung der Studien:

- risk of bias for each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions

### **Ergebnisse**

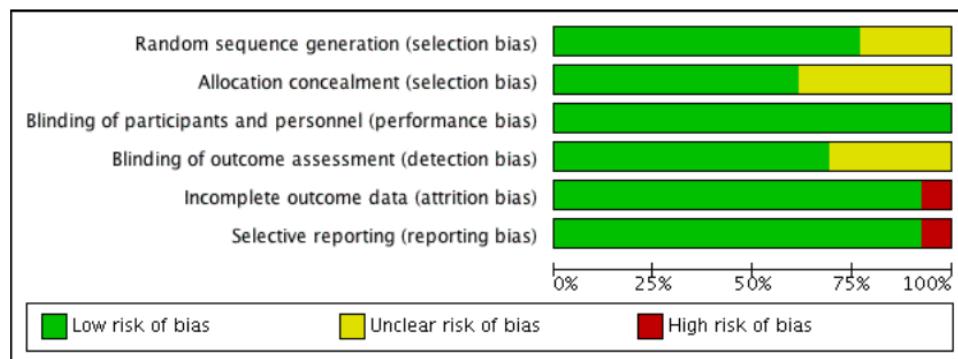
#### Anzahl eingeschlossener Studien:

- 13 studies included in the qualitative synthesis; 12 studies included in the quantitative synthesis

#### 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.



- 

### Studienergebnisse:

- four included studies comparing mepolizumab versus placebo (N=1809)
- four included studies comparing reslizumab versus placebo (N=1764)
- five studies comparing benralizumab versus placebo (N=3232)

Mepolizumab (SC) compared to placebo for asthma					
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	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 <sup>a</sup> Follow-up: range 24 to 32 weeks	The mean rate in the intervention group was 0.55 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 <sup>b</sup> Follow-up: range 24 to 32 weeks	The mean rate in the intervention group was 0.06 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 Follow-up: range 24 to 32 weeks	The mean in the intervention group was -0.42 units fewer (-0.56 fewer to -0.28 fewer)	-	936 (2 RCTs)	⊕⊕⊕○ Moderate <sup>c</sup>
A change of $\geq 0.5$ 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 intervention group was -7.4 units fewer (-9.5 fewer to -5.29 fewer)	-	936 (2 RCTs)	⊕⊕⊕⊕ High	A change of $\geq 4$ is considered the minimum clinically significant difference
Pre-bronchodilator FEV <sub>1</sub> (L) Follow-up: range 24 to 32 weeks	The mean change in the placebo group ranged from 0.086 L ( $\pm 0.031$ ) 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 (2 to 27)	7 per 1000 (2 to 27)	Risk ratio 0.45 (0.11 to 1.80)	936 (2 RCTs)	⊕⊕⊕○ Moderate <sup>d</sup>

\*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<sub>1</sub>: 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

<sup>a</sup>Rounded mean of the rate in the placebo group of the two studies: 1.21 and 1.74.

<sup>b</sup>Rounded mean of the rate in the placebo group of the two studies: 0.10 and 0.20.

<sup>c</sup>The mean difference (-0.42) is smaller than the minimum clinically significant difference (a reduction of 0.5 points).

<sup>d</sup>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)	n 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-up: range 16 weeks to 52 weeks	The mean change in the placebo group ranged from 0.779 to 0.89 units higher <sup>a</sup>	MD 0.28 higher (0.17 higher to 0.39 higher)	-	1164 (3 RCTs)	⊕⊕⊕⊕ High	A change of $\geq 0.5$ 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	The mean change in the placebo group ranged from -0.368 to -0.80 lower <sup>b</sup>	MD -0.25 lower (-0.33 lower to -0.17 lower)	-	1652 (4 RCTs)	⊕⊕⊕⊕ High	A change of $\geq 0.5$ is considered the minimum clinically significant difference

weeks to 52 weeks					
Pre-bronchodilator FEV <sub>1</sub> (L) Follow-up: range 16 weeks to 52 weeks	The mean change in the placebo group ranged from 0.002 L ( $\pm 0.1216$ higher) L to 0.215 ( $\pm 0.0484$ L)	MD 0.11 L higher	-	1652 (4 RCTs)	⊕⊕⊕⊕ High
Serious adverse events Follow-up: range 16 weeks to 52 weeks	91 per 1000 (51 to 102)	72 per 1000	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 (25 to 59)	38 per 1000	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<sub>1</sub>: 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

<sup>a</sup> The mean difference (0.28) is smaller than the minimum clinically significant difference (a reduction of 0.5 points).

<sup>b</sup> The mean difference (-0.25) is smaller than the minimum clinically significant difference (a reduction of 0.5 points)

#### Benralizumab (SC) compared to placebo for asthma

Patient or population: people with asthma

Setting: community

Intervention: benralizumab (SC)

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	n of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with benralizumab (SC)				
Rate of exacerbations requiring systemic corticosteroids Follow-up: range 48 weeks to 56 weeks	The mean rate in the placebo group was 0.98 events per participant per year <sup>a</sup>	The mean rate in the intervention groups was 0.37 fewer events per participant per year (0.44 fewer to 0.29 fewer)	Rate ratio 0.62 (0.55 to 0.70)	2456 (3 RCTs)	⊕⊕⊕⊕ High	
Rate of exacerbations requiring emergency department treatment or admission Follow-up: range 48 weeks to 56 weeks	The mean rate in the placebo group was 0.11 events per participant per year <sup>b</sup>	The mean rate in the intervention groups was 0.04 fewer events per participant per year (0.06 fewer to 0.02 fewer)	Rate ratio 0.68 (0.47 to 0.98)	1537 (2 RCTs)	⊕⊕⊕○ Moderate <sup>c</sup>	There is greater heterogeneity ( $I^2 = 43\%$ ) owing to inclusion of less severe participants in FitzGerald 2016 (a larger proportion who had only suffered one exacerbation the previous year, with correspondingly less potential for exacerbation)
Health-related quality of life (AQLQ) Scale from: 1 to 7 (higher is better) Follow-up: range 48 weeks to 56 weeks	The mean change in the placebo group ranged from 0.98 to 1.31 units higher <sup>c</sup>	MD 0.23 higher	-	1541 (3 RCTs)	⊕⊕⊕⊕ High	A change of $\geq 0.5$ is considered the minimum clinically significant difference

Health-related quality of life (ACQ) Scale from: 0 to 6 (lower is better) Follow up: range 48 weeks to 56 weeks	The mean change in the placebo group ranged (-0.29 lower to -0.11 units)	-	2359 (3 RCTs)	⊕⊕⊕ High	A change of $\geq 0.5$ is considered the minimum clinically significant difference
Pre-bronchodilator FEV <sub>1</sub> (L) Follow-up: range 48 weeks to 56 weeks	The mean change in the placebo group ranged (0.05 L higher to 0.14 L higher)	-	2355 (3 RCTs)	⊕⊕⊕ High	
Serious adverse events Follow-up: range 48 weeks to 56 weeks	135 per 1000 (89 to 136)	109 per 1000 (89 to 136)	RR 0.81 (0.66 to 1.01)	2648 (4 RCTs)	⊕⊕⊕ High
Adverse events leading to discontinuation Follow-up: range 48 weeks to 56 weeks	9 per 1000 (9 to 41)	19 per 1000 (9 to 41)	RR 2.15 (1.02 to 4.57)	2597 (3 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<sub>1</sub>: 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

<sup>a</sup> Rounded mean of the rate in the placebo group of the eosinophilic and non-eosinophilic arms (as applicable) or the three studies: 1.33, 1.21, 0.68, 0.49, 0.93, 1.21.

<sup>b</sup> Rounded mean of the rate in the placebo group of the two studies: 0.18 and 0.04.

<sup>c</sup> The mean difference (0.29) is less than the minimum clinically significant difference ( $\geq 0.5$ ).

## Anmerkung/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.

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## Kew KM et al., 2015 [15].

Long-acting muscarinic antagonists (LAMA) added to inhaled corticosteroids (ICS) versus addition of long-acting beta<sub>2</sub>-agonists (LABA) for adults with asthma.

### 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.

### Methodik

Population: adults (aged 18 years or older) whose asthma is not well controlled with ICS alone

Intervention: LAMA add-on

Komparator: LABA add-on

→ Studies involving the addition of the following LMAs 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

#### 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); 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

Suchzeitraum (Aktualität der Recherche): bis April 2015

Anzahl eingeschlossene Studien/Patienten (Gesamt): 4 RCTs (n= 2049)

Qualitätsbewertung der Studien: Cochrane Risk of Bias Tool; geplante Sensitivitätsanalyse für die primären Endpunkte unter Ausschluss von Studien mit hohem Verzerrungspotential, nicht-publizierten Daten

Heterogenität: I<sup>2</sup> 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).

#### **Ergebnisse**

- 4 Studien eingeschlossen

#### Patientencharakteristika

- Baseline characteristics, with the exception of percentagemale and mean age, were generally poorly reported across studies. Mean percentage predicted FEV1 at baseline was between 66% and 76% in the three studies reporting it (NCT00350207; NCT00565266; Rajanandh 2014; Rajanandh 2015). Mean ages were all between
- 37 and 45 years. The proportion of men and women was fairly balanced within studies reporting this information, and across studies the percentage of men ranged between 33% (NCT00565266) and 65% (LAMA group of Rajanandh 2014).
- All of the studies compared the LAMA, tiotropium, to salmeterol or formoterol, both used as an add-on drug to ICS. NCT01172808 and NCT01172821 were multi-arm twin trials that included separate arms for two doses of tiotropium Respimat, 2.5mcg daily and 5mcg daily. NCT00350207 used tiotropium at 5 mcg daily; NCT00565266, NCT01290874,

Rajanandh 2014, and Rajanandh 2015 used tiotropium HandiHaler 18 mcg daily, but only one of these contributed data to at least one meta-analysis.

**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.

## Studienergebnisse

**Comparison 1. Long-acting muscarinic antagonists (LAMA) add-on versus long-acting beta<sub>2</sub>-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 <sub>1</sub> ) (L)	4		Mean Difference (Random, 95% CI)	0.05 [0.01, 0.09]
6 Peak FEV <sub>1</sub> (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.

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### Kew KM et al., 2016 [14]

Long-acting muscarinic antagonists (LAMA) added to combination long-acting beta<sub>2</sub>-agonists and inhaled corticosteroids (LABA/ICS) versus LABA/ICS for adults with asthma (Review)

#### Fragestellung

To assess the effects of adding a long-acting muscarinic antagonist (LAMA) to combination long-acting beta<sub>2</sub>-agonists (LABA) and inhaled corticosteroids (ICS) in adults whose asthma is not well controlled by LABA/ICS

#### 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:

- 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)
- sekundäre Endpunkte: Exacerbations requiring hospital admission; Lung function (preferably trough forced expiratory volume in one second, or FEV<sub>1</sub>); Asthma control

(measured on a validated scale, e.g. Asthma Control Questionnaire (ACQ), Asthma Control Test); Any adverse events

Recherche/Suchzeitraum:

- bis Januar 2016

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<sup>2</sup> nach Higgins/Thompson

**Ergebnisse**

Anzahl eingeschlossener Studien:

- 3 completed RCTs (n=1197)

Charakteristika der Population:

- Four studies met the inclusion criteria, one of which was withdrawn prior to enrolment (NCT02127697). The other three studies were all multicentre, parallel, double-blind, double-dummy randomised controlled trials sponsored by Boehringer-Ingelheim.
- Kerstjens 2012a and Kerstjens 2012b randomised patients to one of two groups, tiotropium Respimat at a dose of 5 µg once daily or placebo. Ohta 2014 was a three-arm study randomising people to receive one of two doses of tiotropium Respimat, 2.5 µg or 5 µg daily, or placebo.
- Inclusion criteria that were common across the trials were that patients were aged between 18 and 75 years, diagnosed with asthma before age 40 as confirmed at screening with a range of similar lung function requirements, and had a score of at least 1.5 on the ACQ to confirm that it was symptomatic.
- The twin trials were more stringent with criteria relating to the duration and severity of asthma, requiring participants to have at least a five-year history of asthma, at least one exacerbation needing treatment with systemic glucocorticoids in the previous year, and stable high doses of LABA/ICS.
- Ohta 2014 required only a 12-week history of symptomatic asthma, and crucially that participants could be taking stable medium doses of ICS, “alone or in a fixed combination with a LABA, for at least four weeks”.

Qualität der Studien:

- low risk of bias across domains
  - 4 double-blind, double-dummy trials comparing LAMA to placebo, including 1197 people with asthma taking combination LABA/ICS
    - für die quanitative Analyse wurden 3 Studien eingeschlossen

## Studienergebnisse:

### 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 <sub>1</sub> 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; I<sup>2</sup> = 76%).
- high quality evidence showing benefits to lung function (trough FEV<sub>1</sub> and FVC) and potentially small benefits to asthma control. People taking a LAMA add-on were less likely to experience non-serious adverse events.

### Anmerkung/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.

### Kommentare zum Review

- 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

### 3.3 Systematische Reviews

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#### Busse W et al., 2019 [3].

Anti-IL-5 treatments in patients with severe asthma by blood eosinophil thresholds: Indirect treatment comparison.

##### **Fragestellung**

to compare the efficacy of licensed doses of mepolizumab, benralizumab, and reslizumab in patients with SEA, according to baseline blood eosinophil counts.

##### **Methodik**

###### Population:

- patients with SEA aged 12 years or greater

###### Intervention:

- mepolizumab, reslizumab, benralizumab

###### Komparator:

- Placebo als Brückenkopparator

###### Endpunkte:

- Clinically significant exacerbations, defined as an exacerbation requiring treatment with OCSs/systemic corticosteroids (for patients on maintenance OCSs, a >2-fold increase in dose was required) or requiring an emergency department (ED) visit or hospitalization; exacerbations requiring an ED visit/hospitalization; ACQ score (any version); and change from baseline prebronchodilator FEV1. Finally, all included studies had a randomized, double-blind, controlled study design.

###### Recherche/Suchzeitraum:

- Primary data source for this ITC was the published Cochrane by Farne et al. → siehe oben Reference [7]. Additional search on January 2018.

###### Qualitätsbewertung der Studien:

- Vermutlich analog Cochrane Publikation [7].

##### **Ergebnisse**

###### Anzahl eingeschlossener Studien:

- Eleven studies were included: Results of the systematic literature search have previously been reported. From the Cochrane review, 9 studies were identified as eligible for inclusion in this ITC. Additional searches identified 11 further articles, 2 of which presented subgroup analyses relevant for this ITC that were not reported in the primary publications.

###### Charakteristika der Population:

- Across all studies, 3723 patients received either 100 mg of mepolizumab administered subcutaneously Q4W, 3 mg/kg reslizumab Q4W, 30 mg of benralizumab Q8W or placebo. Of the 385 and 551 patients in MENSA and MUSCA, respectively, who received either 100 mg of mepolizumab administered subcutaneously Q4W or placebo.

#### Qualität der Studien:

- K.A.

#### Studienergebnisse:

- All treatments significantly reduced the rate of clinically significant exacerbations and improved asthma control versus placebo in all blood eosinophil count subgroups.
- Mepolizumab reduced clinically significant exacerbations by 34% to 45% versus benralizumab across subgroups (rate ratio >400 cells/mL: 0.55 [95% CI, 0.35-0.87]; >300 cells/mL: 0.61 [95% CI, 0.37-0.99]; and >150 cells/mL: 0.66 [95% CI, 0.49-0.89]; all P < .05) and by 45% versus reslizumab in the 400 cells/mL or greater subgroup (rate ratio, 0.55 [95% CI, 0.36-0.85]; P 5.007).
- Asthma control was significantly improved with mepolizumab versus benralizumab (all subgroups: P < .05) and versus reslizumab in the 400 cells/mL or greater subgroup (P 5 .004).
- Benralizumab significantly improved lung function versus reslizumab in the 400 cells/mL or greater subgroup (P 5 .025).

#### **Anmerkung/Fazit der Autoren**

This ITC of the licensed doses suggests that mepolizumab was associated with significantly greater improvements in clinically significant exacerbations and asthma control compared with reslizumab or benralizumab in patients with similar blood eosinophil counts.

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#### **Xiong XF et al., 2019 [27].**

Efficacy and safety of dupilumab for the treatment of uncontrolled asthma: a metaanalysis of randomized clinical trials.

#### **Fragestellung**

to evaluate the overall efficacy and safety of dupilumab for the treatment of uncontrolled asthma.

#### **Methodik**

##### Population:

- adults/adolescents ( $\geq 12$  years old) diagnosed with uncontrolled asthma
  - Uncontrolled asthma was defined based on current treatment with a medium-to-high-dose inhaled glucocorticoid (fluticasone propionate at a total daily dose of  $\geq 500$   $\mu\text{g}$  or equipotent equivalent), plus up to 2 additional controllers (e.g., a long-acting  $\beta_2$ -agonist or leukotriene receptor antagonist);

##### Intervention:

- dupilumab

##### Komparator:

- placebo

##### Endpunkte:

- lung function (FEV1), he 5-item Asthma Control Questionnaire (ACQ-5) score, fractional exhaled nitric oxide (FENO), AM and PM asthma symptom scores, quality of life (AQLQ), severe exacerbation rate, or adverse events

#### Recherche/Suchzeitraum:

- PubMed, Embase, the Cochrane Library and Chinese Biological Medicine (CBM) databases for articles published up to June 30, 2018

#### Qualitätsbewertung der Studien:

- Cochrane approach

### **Ergebnisse**

#### Anzahl eingeschlossener Studien:

- Five studies involving 3369 patients

#### Charakteristika der Population:

- A single intervention group (dupilumab 300 mg qw and 300 mg q2w) was presented in 2 trials, and the remaining studies included 2 or more interventions (dupilumab 200 mg q2w, 200 mg q4w, 300 mg q2w, 300 mg q4w).
- Outcome reporting varied among the trials. FEV1 was reported in 5 studies
- Severe asthma exacerbations rate was reported in 4 trials. ACQ-5 scores, FENO, and AM and PM asthma symptom scores were reported in 3 trials. AQLQ was reported in 2 trials.

#### Qualität der Studien:

- All trials had a low risk of bias in terms of the 6 domains

#### Studienergebnisse:

- significant improvements with dupilumab in the first-second forced expiratory volume (FEV1) ( $SMD = 4.29$ , 95% CI: 2.78–5.81) and Asthma Quality of Life Questionnaire scores ( $SMD = 4.39$ , 95% CI: 1.44–7.34).
- Dupilumab treatments were also associated with significantly decreased 5-item Asthma Control Questionnaire scores ( $SMD = -4.95$ , 95% CI: -7.30 to -2.60), AM and PM asthma symptom scores ( $SMD = -5.09$ , 95% CI: -6.40 to -3.77;  $SMD = -4.92$ , 95% CI: -5.98 to -3.86, respectively), and severe exacerbation risk ( $RR = 0.73$ ; 95% CI: 0.67–0.79) compared with placebo, with similar incidence of adverse events.

#### **Anmerkung/Fazit der Autoren**

Dupilumab treatment is relatively well-tolerated and could significantly improve FEV1, symptoms, asthma control, and quality of life, and reduced severe exacerbation risk in patients with uncontrolled asthma.

#### *Kommentare zum Review*

- Siehe auch Zayed Y et al. 2018 [28].

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#### **Liu W et al., 2019 [17].**

Adverse events of benralizumab in moderate to severe eosinophilic asthma: A meta-analysis.

## **Fragestellung**

to assess the incidence of these AEs in published randomized controlled trials (RCTs)

## **Methodik**

### Population:

- patients recruited into these studies were diagnosed with moderate to severe eosinophilic asthma;  $\geq 12$  years old

### Intervention:

- intervention must include benralizumab

### Komparator:

- placebo

### Endpunkte:

- AEs

### Recherche/Suchzeitraum:

- Embase, PubMed and Cochrane from inception to September 2018

### Qualitätsbewertung der Studien:

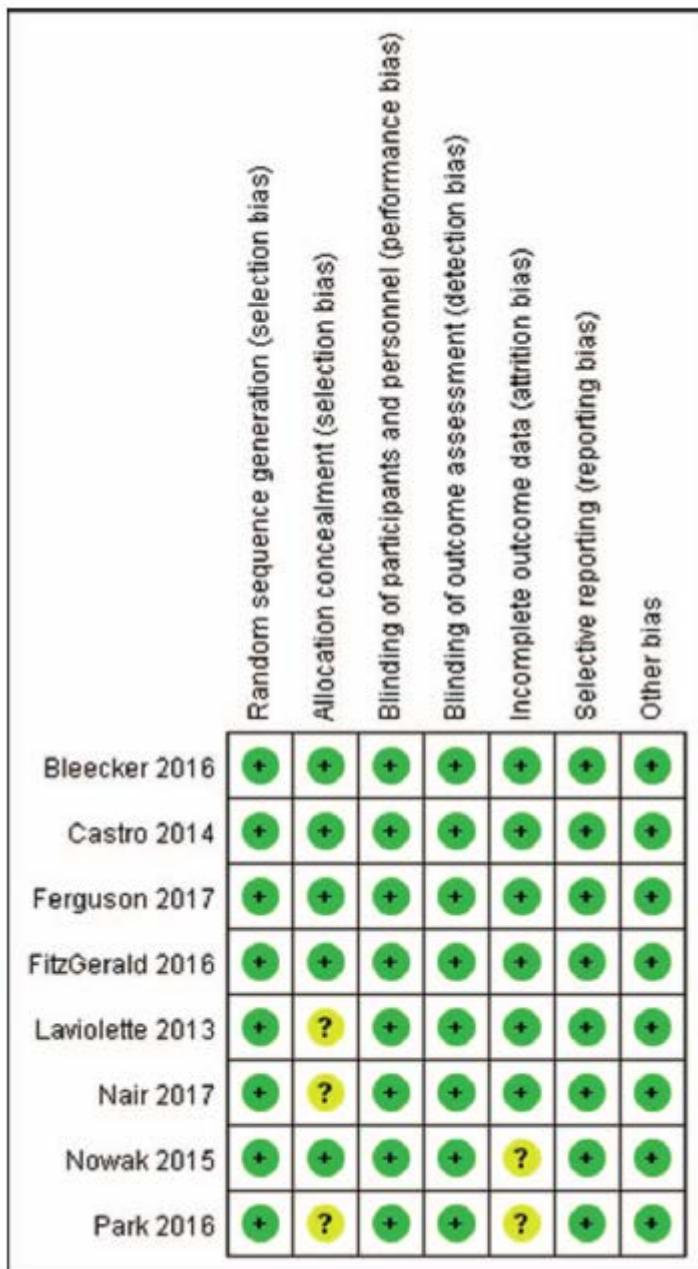


Figure 2. Risk-of-bias summary.

### **Ergebnisse**

#### Anzahl eingeschlossener Studien:

- Eight RCTs with 3788 patients

#### Charakteristika der Population:

- Of these 3788 patients, 2277 received benralizumab treatment and the remaining 1511 received placebo, and a comparative analysis of different dose groups was included. All patients enrolled in the trials were from various experimental centers in a number of countries. All patients had a history of physician-diagnosed asthma requiring treatment with

medium-to-high dose ICS or ICS/LABA for at least 1 year or 2 years prior to screening, and post-bronchodilator reversibility of airflow obstruction  $\geq 12\%$ .

Qualität der Studien:

- Cochrane Collaboration's tool

Studienergebnisse:

- Overall AEs (6 trials):
  - 7.61% (1448/2008) of patients in the benralizumab group developed bronchitis as compared to 10.04% (799/1063) of patients in the placebo group.
  - Fewer patients treated with benralizumab vs placebo experienced overall AEs (RR 0.94, 95% CI 0.90–0.98, P=.03, I<sup>2</sup>=14%).
- Serious AEs (SAEs) (7 trials):
  - benralizumab had a lower chance of suffering SAEs than patients in the placebo group (RR 0.82, 95% CI 0.68–0.98, P=.03, I<sup>2</sup>= 0%)
- Asthma (7 trials):
  - A statistically significant difference in worsening asthma between the patients receiving benralizumab and patients receiving placebo was observed (RR 0.72, 95% CI 0.61–0.85, P=.0001, I<sup>2</sup>=30%). Thus, the benralizumab group had a lower risk of worsening asthma than the placebo group
- Bronchitis (5 trials):
  - The benralizumab group had a lower probability of bronchitis than the placebo group (RR 0.76, 95% CI 0.59–0.96, P=.02, I<sup>2</sup>=0%)
- Sinusitis (5 trials):
  - benralizumab group had a lower probability of experiencing sinusitis than the placebo group (RR 0.65, 95% CI 0.49–0.86, P=.002, I<sup>2</sup>=0%)
- Headache (7 trials):
  - The benralizumab group was more likely to suffer headache than the placebo group (RR 1.42, 95% CI 1.07–1.87, P=.01, I<sup>2</sup>=0%)
- Pyrexia (4 trials):
  - a higher odds of pyrexia in the benralizumab group as compared to the placebo group (RR 2.26, 95% CI 1.32–3.87, P=.003, I<sup>2</sup>=0%)
- Other AEs: No increased incidence of death, hypersensitivity, injection-site reactions, nasopharyngitis, rhinitis, upper respiratory tract infection, influenza, cough, nausea, back pain or arthralgia was observed with benralizumab compared with placebo.

**Anmerkung/Fazit der Autoren**

Benralizumab reduced the risk of SAEs, asthma exacerbation, bronchitis and sinusitis, and aggravated the risk of headache and pyrexia. Other AEs were comparable between the benralizumab group and placebo group. Therefore, benralizumab is a relatively safe drug, but vigilance regarding AEs is imperative during long-term treatment.

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**Bourdin A et al., 2018 [1].**

Matching-adjusted indirect comparison of benralizumab versus interleukin-5 inhibitors for the treatment of severe asthma: a systematic review.

## **Fragestellung**

to perform a MAIC of benralizumab versus IL-5-directed monoclonal antibodies for the treatment of patients with severe, uncontrolled asthma and with an eosinophilic phenotype.

## **Methodik**

### Population:

- patients with severe, uncontrolled asthma receiving medium- or high-dosage ICS plus an additional controller medication

### Intervention/Komparator

- Indirekter Vergleich
  - IL-5Ra/anti-IL-5 treatments with placebo

### Endpunkte:

- annual rate of clinically significant exacerbations, annual rate of exacerbations requiring emergency department (ED) visit or hospitalisation, and pre-bronchodilator forced expiratory volume in 1 s (FEV1)

### Recherche/Suchzeitraum:

- MEDLINE, EMBASE, MEDLINE In-Process and CENTRAL databases from inception to August 2016

### Qualitätsbewertung der Studien:

- risk of bias was assessed using a NICE checklist

## **Ergebnisse**

### Anzahl eingeschlossener Studien:

- In total identified: 32. For analysis:
  - The evidence networks generated for the placebo-anchored comparison of benralizumab versus mepolizumab included the benralizumab SIROCCO and CALIMA trials and the mepolizumab MENSA and DREAM trials (siehe Studiencharakteristika unten).
  - The evidence network for the placebo-anchored comparison of benralizumab versus reslizumab included the benralizumab SIROCCO and CALIMA trials and the reslizumab Study 3082 and Study 3083 trials.
  - In studies with several treatment arms, only active treatment arms that used licenced (European and USA) dosages were included.

## Charakteristika der Population:

**Table S4. Summary of study characteristics of benralizumab, mepolizumab, and reslizumab studies**

Study characteristics	Benralizumab		Mepolizumab		Reslizumab	
	SIROCCO [3]	CALIMA [5]	MENSA [16]	DREAM [18]	Study 3082 [26]	Study 3083 [26]
Publication type	Journal and CSR	Journal and CSR	Journal and CSR	Journal and CSR	Journal	Journal
Interventions	Benralizumab 30 mg Q4W SC	Benralizumab 30 mg Q4W SC	Mepolizumab 75 mg Q4W IV	Mepolizumab 75 mg Q4W IV	Reslizumab 3.0 mg/kg IV	Reslizumab 3.0 mg/kg IV
	Benralizumab 30 mg Q8W SC	Benralizumab 30 mg Q8W SC	Mepolizumab 100 mg Q4W SC	Mepolizumab 250 mg Q4W IV	Placebo	Placebo
	Placebo	Placebo	Placebo	Mepolizumab 750 mg Q4W IV	-	-
	-	-	-	Placebo	-	-
Phase	III	III	III	IIb	III	III
Sample size	1205 (805) <sup>a</sup>	1306 (734) <sup>a</sup>	580	308	489	464
Method of randomisation	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate
Blinding status	Double-blind	Double-blind	Double-blind	Double-blind	Double-blind	Double-blind
Treatment duration	48 weeks	56 weeks	32 weeks	52 weeks	52 weeks	52 weeks
Primary outcome	• Annual rate ratio of asthma exacerbations for patients receiving high-dose ICS + LABA vs placebo with baseline blood EOS ≥300 cells/µL	• Annual rate ratio of asthma exacerbations for patients receiving high-dose ICS + LABA vs placebo with baseline blood EOS ≥300 cells/µL	• Rate of clinically significant exacerbations	• Rate of clinically significant exacerbations	• The frequency of clinical asthma exacerbations per patient during the 52 week treatment period, with events adjudicated by an independent review committee	• The frequency of clinical asthma exacerbations per patient during the 52 week treatment period, with events adjudicated by an independent review committee

The highlighted cells indicate differences across the trials.

\*Number in parenthesis represents patients for benralizumab Q8W and placebo arms.

**TABLE 1 Comparison of baseline characteristics of patients included in benralizumab (SIROCCO, CALIMA) and mepolizumab (MENSA, DREAM) studies**

Characteristics	SIROCCO		CALIMA (only high-dosage ICS subgroup)		MENSA		DREAM	
	Benralizumab Q8W	Placebo	Benralizumab Q8W	Placebo	Mepolizumab 100 mg SC	Mepolizumab 75 mg IV	Placebo	Mepolizumab 75 mg IV
<b>Patients n</b>	398	407	364	370	194	191	191	153
<b>Age mean±so years</b>	47.6±14.5	48.7±14.9	50.1±13.3	49.8±14.3	51.2±14.55	50.0±14.03	49.2±14.26	50.2±11.3
<b>Male sex %</b>	36.7	33.9	38.2	40.3	40.0	45.0	44.0	32.0
<b>Race %</b>								
White	72.1	74.2	85.2	86.8	77.0	79.0	77.0	91.0
Black	3.8	3.9	3.6	3.2	4.0	3.0	2.0	3.0
Asian	12.6	12.3	11.0	10.0	18.0	17.0	20.0	5.0
Other	11.6	9.6	0.3	0.0	1.0	1.0	1.0	0.0
<b>BMI mean±so kg·m<sup>-2</sup></b>	28.21±6.18	28.93±7.07	29.0±6.5	29.25±6.54	27.60±5.58	27.68±5.68	28.04±5.58	28.4±6.0
<b>FEV<sub>1</sub> % pred mean</b>	56.1 <sup>#</sup>	56.6 <sup>#</sup>	56.9	57.5	59.3	61.4	62.4	60 <sup>#</sup>
<b>Morning PEF mean L·min<sup>-1</sup></b>	233.12	230.83	241.85	242.16	255.3	268.6	277	-
<b>FEV<sub>1</sub>/FVC %</b>	65	66	64	65	63	64	64	68
<b>FEV<sub>1</sub> pre-bronchodilator L</b>	1.68	1.66	1.72	1.76	1.73	1.85	1.86	1.81 <sup>#</sup>
<b>Reversibility %</b>	27.2	25.5	25.1	27.2	27.9 <sup>#</sup>	25.4 <sup>#</sup>	27.4 <sup>#</sup>	22.6 <sup>¶</sup>
<b>ACQ score<sup>*</sup></b>	2.8	2.87	2.82	2.73	2.26	2.12	2.28	2.2
<b>Exacerbations in previous year</b>								
Mean n	2.8	3	2.7	2.8	3.8	3.5	3.6	>3 <sup>§</sup>
2 exacerbations %	63.3	60	62.9	63.5	38	43	47	46
≥3 exacerbations %	36.68	40	36.81	36.49	61.86	57.07	52.88	54
<b>Never smokers %</b>	82.2	80.6	78.02 <sup>¶</sup>	78.92 <sup>¶,f</sup>	74 <sup>¶,f</sup>	73 <sup>¶</sup>	70 <sup>¶</sup>	80 <sup>¶</sup>
<b>OCS use %</b>	17.8	16.2	10.71 <sup>#</sup>	11.08 <sup>¶,f</sup>	27 <sup>¶,f</sup>	25 <sup>#</sup>	23 <sup>#</sup>	30.07 <sup>#</sup>
<b>EOS ≥300 cells·µL<sup>-1</sup> %</b>	67.08	65.6	65.6	67.02	51.5	53.4	55.4	56.2
<b>EOS &lt;300 cells·µL<sup>-1</sup> %</b>	32.9	34.3	34.3	32.9	47.4	45.02	43.4	43.7
<b>EOS count mean cells·µL<sup>-1</sup></b>	469.8	456.5	463.4	490.8	290 <sup>##</sup>	280 <sup>##</sup>	320 <sup>##</sup>	250 <sup>##</sup>
<b>IgE concentration IU·mL<sup>-1</sup></b>	-	-	-	-	149.72 <sup>##</sup>	180.32 <sup>##</sup>	150.12 <sup>##</sup>	-
<b>Atopic status %</b>	61.3	56.5	61.5	63.0	-	-	-	51.0
<b>Nasal polyps %</b>	19.0	19.0	16.8	18.1	14.4	16.7	17.2	7.0

Data in bold indicate differences across benralizumab and mepolizumab trials. For cells with no data listed, none were available. ICS: inhaled corticosteroid; Q8W: every 8 weeks (first three doses every 4 weeks); SC: subcutaneous; IV: intravenous; BMI: body mass index; FEV<sub>1</sub>: forced expiratory volume in 1 s; PEF: peak expiratory flow; FVC: forced vital capacity; ACQ: Asthma Control Questionnaire; OCS: oral corticosteroid; EOS: eosinophil. <sup>#</sup>: data extracted from publications rather than clinical study reports; <sup>¶</sup>: data reported at screening visit; <sup>\*</sup>: ACQ-6 in SIROCCO, CALIMA and DREAM, and ACQ-5 in MENSA; <sup>§</sup>: calculated from the reported frequency of exacerbations; <sup>f</sup>: calculated from the reported subgroup data; <sup>##</sup>: geometric means.

## Qualität der Studien:

- “ Only phase 3 studies were included“

## Studienergebnisse:

- After matching adjustment, benralizumab and mepolizumab reduced exacerbations versus placebo by 52% and 49%, respectively (rate ratio [RR] 0.94, 95% CI 0.78–1.13; n=1524)

and reduced the rate of exacerbations requiring hospitalisation/emergency department visit by 52% and 52%, respectively (RR 1.00, 95% CI 0.57–1.75; n=1524).

- Benralizumab and mepolizumab similarly improved pre-bronchodilator forced expiratory volume in 1 s at 32 weeks (difference 0.03 L, 95% CI –0.06–0.12; n=1443).
- Benralizumab and reslizumab patient populations were too dissimilar to generate a sufficient effective sample size to produce a reliable estimate for MAIC.

#### Anmerkung/Fazit der Autoren

MAIC is an accepted method for comparing treatments in lieu of head-to-head trials and is less subject to biases than standard ITC. To our knowledge, this is the first MAIC comparing monoclonal antibodies for the treatment of severe asthma. The MAIC demonstrated that, after adjustment for baseline population characteristics that differed across benralizumab versus mepolizumab trials, reductions in asthma exacerbation rates were similar, and improvements in FEV1 were slightly better but not statistically significant at all time points tested. Comparisons with reslizumab could not be performed because of insufficient ESS.

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#### Sobieraj DM et al., 2018 [22].

Association of Inhaled Corticosteroids and Long-Acting Muscarinic Antagonists With Asthma Control in Patients With Uncontrolled, Persistent Asthma A Systematic Review and Meta-analysis

+

#### Sobieraj DM et al., 2018 [23].

Intermittent Inhaled Corticosteroids and Long-Acting Muscarinic Antagonists for Asthma

#### Fragestellung

To conduct a systematic review and meta-analysis of the effects associated with LAMA vs placebo or vs other controllers as an add-on therapy to inhaled corticosteroids and the use of a LAMA as add-on therapy to inhaled corticosteroids and long-acting  $\beta$ -agonists (LABAs; hereafter referred to as triple therapy) vs inhaled corticosteroids and LABA in patients with uncontrolled, persistent asthma

#### Methodik

##### Population:

- patients 12 years and older with uncontrolled, persistent asthma

##### Intervention vs Komparator:

- LAMA vs placebo or vs another controller as an add-on therapy to inhaled corticosteroids or that compared triple therapy vs inhaled corticosteroids and LABA

##### Endpunkte:

- asthma exacerbations (systemic corticosteroid use, hospitalization, emergency department visits, intensive care or intubation, or as defined by the study)
- mortality (all cause or asthma-specific),
- spirometry (measured as peak, trough, and area under the curve [AUC] values for forced expiratory volume in the first second [FEV1], forced vital capacity [FVC], and FEV1/FVC);

- asthma control (Asthma Control Test [ACT] or Asthma Control Questionnaires [ACQs; 5-, 6-, or 7-item]), asthma-related quality of life (Asthma Quality of Life Questionnaire [AQLQ], MiniAQLQ, and AQLQ for 12 y and older [AQLQ +12]),
- health care utilization (additional medication use, additional health resource use related to the intervention)

Recherche/Suchzeitraum:

- MEDLINE, EMBASE, Cochrane databases, and clinical trial registries (earliest date through November 28, 2017).

Qualitätsbewertung der Studien:

- Cochrane Collaboration's Risk of Bias Tool for RCTs

## Ergebnisse

Anzahl eingeschlossener Studien:

- 15 RCTs (n=7122)

Charakteristika der Population:

- All trials enrolled adults 18 years or older with the exception of 2 trials<sup>22,28</sup> that were exclusively focused on children and adolescents aged 12 to 17 years.
- Sample sizes for individual studies ranged from 21029 to 1071 participants.<sup>18</sup> Eight RCTs compared LAMA vs placebo as add-on therapy to inhaled corticosteroids.<sup>17-22,29</sup>
- Five of these trials<sup>17-19,29</sup> also included a LABA group and were also used to evaluate the effect of LAMA vs LABA as add-on therapy to inhaled corticosteroids. An additional 3 trials<sup>23-25</sup> compared LAMA with another controller, including LABA, doxofylline, and montelukast. Four RCTs evaluated triple therapy vs inhaled corticosteroids and LABA. Trials ranged from 15 days<sup>19</sup> to 18 months<sup>25</sup> in duration.
- Trials included in this systematic review defined uncontrolled asthma based on the ACQ score. However, this is only 1 of many criteria recommended for assessment.<sup>1</sup> Likewise, although all patients were considered to have persistent asthma given their use of inhaled corticosteroids maintenance therapy, whether patients had mild, moderate, or severe persistent asthma was left to the reporting of the study authors.

Qualität der Studien:

- Most RCTs had a low risk of bias for random sequence generation (13 [86.7%]), allocation concealment (12 [80%]), incomplete data reporting (14 [93.3%]), selective reporting (12 [80%]), and other types of bias (15 [100%]). Three studies (20%) had a high risk of bias for blinding of participants and personnel and 2 studies (13.3%) for blinding of study outcomes.

## Studienergebnisse:

LAMA vs Other Controllers as Add-on Therapy to Inhaled Corticosteroids

- Comparing LAMA with LABA as add-on therapy to inhaled corticosteroids, there was no statistically significant association of LAMA with
  - the risk of exacerbation requiring systemic corticosteroid (RR, 0.87 [95% CI, 0.53 to 1.42]; RD, 0.00 [95% CI, -0.02 to 0.02])

- in asthma worsening (RR, 1.00 [95% CI, 0.84 to 1.20]; RD, 0.00 [95% CI, -0.05 to 0.04]), or in the composite outcome including oral steroid use or increase in asthma medication (RR, 0.60 [95% CI, 0.15 to 2.42]; RD, -0.03 [95% CI, -0.12 to 0.06]).
- No deaths occurred in 3 RCTs and in the fourth trial 3 of 532 participants (0.6%) died in the LAMA group, 2 of these deaths were considered asthma-related (0.4%) whereas no deaths occurred in the LABA group.
- LAMA had no significant associations with ACQ scores with 1 trial reporting ACQ-6 score, 2 trials reporting ACQ-7 scores, and 2 trials reporting ACQ-7 responder analysis.
- No significant associations were found in measures of spirometry including the most frequently reported lung function measures of FEV1 trough, FEV1% predicted, and FVC trough with LAMA use
- No significant associations were found for AQLQ score

#### Triple Therapy vs Inhaled Corticosteroids and LABA

- Triple therapy was not significantly associated with the risk of exacerbation requiring systemic corticosteroids vs inhaled corticosteroids and LABA when the inhaled corticosteroid dose remained the same (RR, 0.84 [95% CI, 0.57 to 1.22]; RD, -0.01 [95% CI, -0.08 to 0.07]) (Figure 2A)
- it was significantly associated with a lower risk of asthma worsening (RR, 0.78 [95% CI, 0.72 to 0.86]; RD, -0.01 [95% CI, -0.22 to 0.01])
- (eFigure 3 in the Supplement) (Table 3).
- Two studies reported exacerbations requiring hospitalization and neither found a significant association at 48 weeks.
- No deaths occurred in the 3 trials included in this analysis, 2 of which were 48 weeks in duration and the third being 12 weeks in duration.
- No significant associations with ACQ-7 scores were found with triple therapy vs inhaled corticosteroids and LABA (Figure 2B). No consistent association for triple therapy on ACQ response was seen across studies (Table 3).
- Triple therapy was associated with improvements in some measures of spirometry, including FEV1 trough (MD, 0.07 [95% CI, 0.01 to 0.14]) and measures of FVC (peak MD, 0.11 [95% CI, 0.05 to 0.17]; trough MD, 0.09 [95% CI, 0.03 to 0.15]); AUC MD, 0.10 [95% CI, 0.04 to 0.17]) (Figure 3A, eFigures 6-10 in the Supplement).
- No significant association with AQLQ score or AQLQ score response was seen with triple therapy.
- Triple therapy was not significantly associated with improvements in rescue medication use vs combined inhaled corticosteroids and LABA therapy (Figure 3B).

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### **Anmerkung/Fazit der Autoren**

The association of LAMA with benefit may not be greater than that with LABA. Triple therapy was not associated with a lower risk of exacerbations.

### **Tian BP et al., 2017 [24].**

Efficacy and safety of benralizumab for eosinophilic asthma: A systematic review and meta-analysis of randomized controlled trials

### **Fragestellung**

We conducted a systematic review of the literatures to provide a summary of the relevant studies and to assess the efficacy and safety of administering benralizumab on clinical exacerbation, lung function, life quality, and adverse events (AEs) in asthma patients.

### **Methodik**

#### Population:

- Eosinophilic asthma patients

#### Intervention:

- benralizumab

#### Komparator:

- placebo

#### Endpunkte:

- symptom control, lung function or AEs

### Recherche/Suchzeitraum:

- PubMed» Embase, and Cochrane Controlled Trials Register databases until May 31, 2017

### Qualitätsbewertung der Studien:

- Cochrane risk of bias

## **Ergebnisse**

### Anzahl eingeschlossener Studien:

- 7 articles on 9 RCTs (n=2321 patients)

### Charakteristika der Population:

- The subjects were patients with uncontrolled severe or severe asthma in five articles [21, 29-32], asthma exacerbation in one article [119], and eosinophilic asthma in two studies from one article [20].
- Participants received intravenous benralizumab in two studies [20, 21], and the others received subcutaneous injections.

### Qualität der Studien:

Table 2. Risk of bias of the included studies.

Source	Random sequence generation	Allocation concealment	Blinding of participants & personal	Blinding of outcomes assessment	Incomplete outcome data	Selective reporting
Lavoielette (2013)						
Cohort 1	Yes	Yes	Yes	Yes	Yes	Yes
Cohort 2	Yes	Yes	Yes	Yes	Yes	Yes
Castro (2014)	Yes	Yes	Yes	Yes	Yes	Yes
Nowak (2015)	Yes	Unclear	Yes	Yes	Yes	Yes
Park (2016)	Yes	Unclear	Yes	Yes	Yes	Yes
FitzGerald (2016)	Yes	Yes	Yes	Yes	Yes	Yes
Bleecker (2016)	Yes	Yes	Yes	Yes	Yes	Yes
Nair (2017)	Yes	Yes	Yes	Yes	Yes	Yes

## **Studienergebnisse:**

### Asthma Exacerbations.

- All six studies defined asthma exacerbation based on the unscheduled use of rescue medication.
- Among them, five studies defined asthma exacerbation as the use or increase dose of systemic steroids for at least three days [28-32], and one defined the criterion as an uncontrolled symptom after the use of rescue albuterol or corticosteroids within 2 h, and required a visit to the emergency room [19].

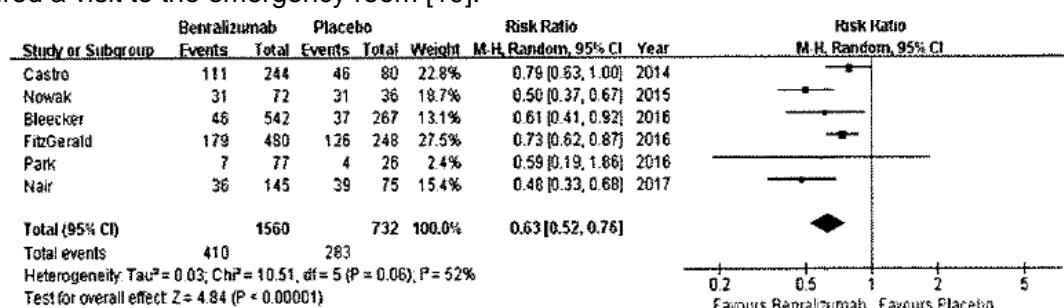


Figure 2. The effect of benralizumab versus placebo on exacerbations.

### FEV1% changes from basefine

- Three studies assessed the responsiveness of FEV1 (forced expiratory volume in 1 sec) % of predicted value
- No significant difference was observed between the benralizumab and placebo groups in changes from baseline of FEV1% of the predicted value (SMD: -0.10, 95% CI: -0.31 to 0.10,  $p = 0.33$ ). No statistical heterogeneity was observed ( $I^2 = 0\%$ ,  $p = 0.38$ ).
- Notably, two phase 3 studies (FitzGerald, CALIMA & Bleeker, SIROCCO) suggested that eosinophilic asthma subjects who were treated with benralizumab exhibited significant increases in the pre-bronchodilator FEV1 compared to placebo for patients receiving high-dosage ICSs plus LABA with baseline blood eosinophil counts of at least 300 cells/ $\mu$ L on both the Q4W (30 mg, every 4 weeks) and Q8W (30 mg, every 8 weeks) therapeutic schedules [29,30].
- For patients with baseline eosinophil counts lower than 300 cells/ $\mu$ L, an improvement in FEV1 after benralizumab treatment was noted in Castro et al's study (100 mg) but not in the trials conducted by FitzGerald et al. And Bleeker et al. [21, 29, 30].
- For the severe asthma, benralizumab treatment significantly increased the FEV1 at 20 weeks but not at over the entire 28-week trial period versus placebo [31].

### Asthma Control Questionnaire (ACQ) score

- Although several trials described the ACQ scores, the ACQ data of four RCTs with 755 participants (544 in the benralizumab treatment group and 217 in the placebo-control group) could be analyzed together [19, 21, 31, 32].
- The findings from the meta-analysis suggested similar outcomes for the ACQ changes from baseline between the benralizumab and control groups (SMD: -0.10, 95% CI: -0.26 to 0.06,  $p = 0.22$ ) in eosinophilic asthmatics.
- No significant heterogeneity was observed among the studies ( $I^2 = 32\%$ ,  $f = 0.22$ ) (Figure S2).

### Asthma control and Quality of Life Assessment (AQLQ)

- In the eosinophilic asthma subpopulations, life quality was assessed using the AQLQ questionnaire [19, 21].
- The results from the pooled statistical analysis from these two studies showed no obvious improvement for the AQLQ score in the benralizumab arm compared to the placebo arm (SMD: -0.11, 95% CI: -0.32 to 0.10,  $p = 0.3$ ), and statistical heterogeneity was not found ( $I^2 = 0\%$ ,  $p = 0.58$ ).
- However, as reported by three phase three clinical trials [29-31], health-related quality of life benefited from benralizumab treatment for the 30 mg Q8 schedule but not for the 30 mg Q4W schedule.

### Adverse events

- Although seven studies included AEs, six studies reported total AEs that could be analyzed [20, 21, 29-32].

- A total of 1,216 of 1,646 patients suffered AEs in the benralizumab arms compared to 622 of the 847 controls in asthmatics who had a peripheral blood eosinophil count of at least 300 cells/µL, with a RR of 1.00 (95% CI: 0.95-1.05, p = 0.96).
- Statistical heterogeneity was not observed among the studies (/ ^ 40%, p == 0.13).

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### **Anmerkung/Fazit der Autoren**

In summary, we found that the use of benralizumab, a humanized monoclonal antibody against IL-5Ro', appears to be safe for controlling exacerbations but may not improve the lung function, ACQ or AQLQ score. These findings provided a foundation for the reasonable use of benralizumab for asthma patients. Additionally, larger samples and more high-quality studies are required to further investigate the efficacy and safety of benralizumab in asthma.

### Fragestellung

We conducted a meta-analysis of randomized controlled trials (RCTs) to assess the overall efficacy and safety of anti-interleukin 5 treatments on eosinophilic asthma.

### Methodik

#### Population:

- adults/ adolescents (12 years or older) with a diagnosis of eosinophilic asthma,
- eosinophilic inflammation was shown by one or more criteria at study entry or in the previous year: a sputum eosinophil count  $\geq 2.5\%$  or the eosinophil/lymphocyte and eosinophil/neutrophil (ELEN; a surrogate blood-based marker of sputum eosinophilia) index was positive, an exhaled nitric oxide concentration (FENO)  $\geq 50$  ppb, and an asthma-related peripheral blood eosinophil count  $\geq 300 \mu\text{L}$

#### Intervention:

anti-interleukin 5 therapy at any dose

#### Komparator:

others

#### Endpunkte:

lung function, asthma exacerbations, asthma control and quality-of-life scores, and adverse events

#### Recherche/Suchzeitraum:

PubMed, Embase, the Cochrane Library, and the Chinese Biological Medicine (CBM) database for articles published up to June 2016

#### Qualitätsbewertung der Studien:

Cochrane risk of bias

### Ergebnisse

#### Anzahl eingeschlossener Studien:

12 RCTs (3340 patients)

#### Charakteristika der Population:

- The sample sizes ranged from 20 to 621 subjects.
- Of these, five studies used mepolizumab [7–11], four reslizumab [19–22], and three benralizumab [12, 23, 24].
- Treatment duration ranged from 1 day to 52 weeks and follow-up ranged from 12 to 52 weeks.
- The mean age of patients was 46.8 years old. [...]
- Five studies included severe eosinophilic asthmatics [8–11, 19], three studies included refractory or uncontrolled eosinophilic asthmatics [7, 20, 22], and the remaining studies did not specify asthma severity [12, 21, 23, 24].

### Qualität der Studien:

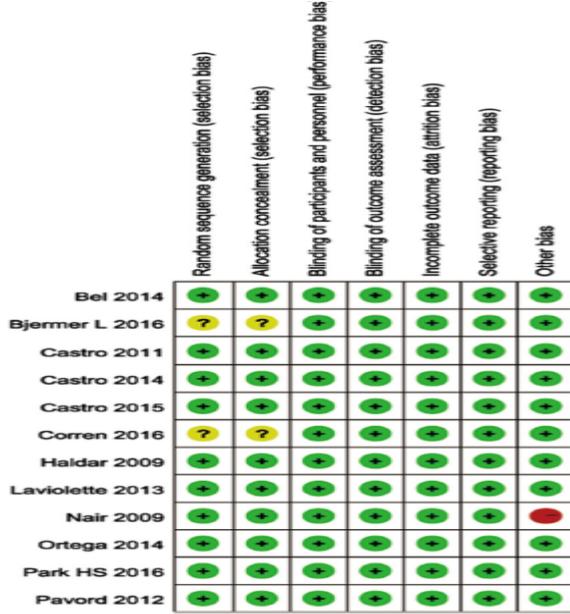


Fig. 8 Risk of bias summary of included studies

### Studienergebnisse:

#### FEV1

- Nine trials reported the data on FEV1.
- Mepolizumab was used in four studies showed significant effect on FEV1 ( $MD = 0.09$ ; 95 % CI, 0.03 to 0.14;  $P = 0.002$ ).
- Reslizumab was reported in four studies, also could significantly improve FEV1 ( $MD=0.15$ , 95 % CI, 0.09 to 0.22;  $P < 0.001$ ).
- Benralizumab was used in only one study ( $MD = 0.14$ , 95 % CI, 0.02 to 0.26;  $P = 0.02$ ).
- Overall, anti-interleukin 5 treatment were associated with significant improvements in FEV1 ( $MD = 0.12$ ; 95 % CI, 0.08 to 0.16;  $P < 0.001$ ) (Fig. 2), with minimal heterogeneity ( $I^2 = 15\%$ ,  $P = 0.3$ ),

#### Asthma Quality-of-Life Questionnaire (AQLQ)

- Five trials provided data about AQLQ scores.
- The pooled analysis showed anti-interleukin 5 treatment was associated with a significant increase in AQLQ scores ( $MD = 0.23$ ; 95 % CI, 0.13–0.34;  $P < 0.001$ ), with no significant heterogeneity ( $I^2 = 0\%$ ;  $P = 0.81$ ).
- AQLQ scores improved both in
  - mepolizumab treatment ( $MD = 0.18$ ; 95 % CI, 0.01–0.36;  $P = 0.04$ )
  - reslizumab ( $MD = 0.27$ ; 95 % CI, 0.13–0.42;  $P < 0.001$ ).
  - Benralizumab only used in one study ( $MD = 0.21$ ; 95 % CI, −0.12–0.54;  $P = 0.22$ ).

#### Asthma Exacerbations

- Six studies were included.

- Overall, compared with placebo, asthma exacerbations risk was significantly decreased with anti-interleukin 5 treatment ( $RR = 0.52$ ; 95 % CI, 0.46 to 0.59;  $P < 0.001$ ), and there was no heterogeneity among studies ( $I^2 = 0 \%$ ,  $P = 0.5$ ).
- When looking at subgroups, mepolizumab ( $RR = 0.55$ ; 95 % CI, 0.47 to 0.64;  $P < 0.001$ ) and reslizumab ( $RR = 0.46$ ; 95 % CI, 0.37 to 0.58;  $P < 0.001$ ) were also linked to markedly lower asthma exacerbations.

### Adverse Events

- Eight studies mentioned adverse events.
- Anti-interleukin 5 treatment was associated with a trend of lower adverse events incidence ( $RR = 0.93$ ; 95 % CI, 0.89 to 0.97;  $P = 0.001$ ), with no heterogeneity ( $I^2 = 0 \%$ ,  $P = 0.55$ ).
- In subgroup analysis, however, we found no significant differences in both mepolizumab ( $RR = 0.96$ ; 95 % CI, 0.9–1.03;  $P = 0.3$ ) and benralizumab treatment groups ( $RR = 0.91$ ; 95 % CI, 0.81–1.02;  $P = 0.09$ ).
- Only treatment with reslizumab was associated with a trend of lower adverse events incidence ( $RR = 0.92$ ; 95 % CI, 0.87–0.97;  $P = 0.003$ )
- The incidence of serious adverse events was low in the antiinterleukin 5 treatment group (1–16 %). Common adverse events were nasopharyngitis, headache, asthma worsening, injection-site reactions and upper respiratory tract infection

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 51) 21.  
 52) Corren J, Weinstein S, Janka L, Zangrilli J, Garin M (2016) Phase 3 study of reslizumab in patients with poorly controlled asthma: effects across a broad range of eosinophil counts. *Chest*. doi: 10.1016/j.chest.2016.03.018 PubMedCrossRefGoogle Scholar  
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- 58) Park HS, Kim MK, Imai N, Nakanishi T, Adachi M, Ohta K (2016) A phase 2a study of benralizumab for patients with eosinophilic asthma in South Korea and Japan. *Int Arch Allergy Immunol* 169(3):135–145. doi: 10.1159/000444799

### **Anmerkung/Fazit der Autoren**

In summary, the current meta-analysis indicated that antiinterleukin 5 treatment was well tolerated and could significantly improve FEV1, quality of life, and reduced asthma exacerbation risk in patients with eosinophilic asthma. Therefore, the humanized anti-interleukin 5 monoclonal antibodies may be effective and safe for eosinophilic asthma. The results highlight the importance of selection asthma phenotypes could derive clinical benefit from anti-interleukin 5 therapy. Nasopharyngitis was the most frequently reported adverse event in either study involving anti-interleukin 5 treatments, and benralizumab needs more data to support its safety profile.

**Li J et al., 2017 [16].**

### **Fragestellung**

The efficacy and safety of reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: A systematic review and meta-analysis

### **Methodik**

#### Population:

inadequately controlled, eosinophilic asthma

#### Intervention vs Komparator:

Reslizumab vs. others

#### Endpunkte:

Asthma exacerbation, a forced expiratory volume in 1 s (FEV1), Asthma Control Questionnaire (ACQ) score, blood eosinophil counts, the proportion of individuals who withdrawn due to adverse event (AE) and Upper respiratory AEs.

#### Recherche/Suchzeitraum:

Medline, Embase and Cochrane Controlled Trials Register databases until May 2016

#### Qualitätsbewertung der Studien:

Cochrane risk of bias

### **Ergebnisse**

#### Anzahl eingeschlossener Studien:

4 articles [16–19], reporting data from a total of 5 RCTs that compared reslizumab with placebo

## Charakteristika der Population:

**Table 1.** Study and patient characteristics.

Study	Therapy in experimental group	Therapy in control group	Country	Sample size		Administration method	Duration of treatment	Dosage (mg)	Inclusion population
				Experimental	Control				
Castro M 2015 [16]	Reslizumab	Placebo	Asia, Australia, North America, South America, South Africa, and Europe	245/232	244/232	intravenous	16 weeks	(3.0 mg/kg)	Patients aged 12–75 with at least one blood eosinophil count of 400 cells per $\mu\text{L}$ or higher and inadequately controlled asthma
Castro M 2011 [17]	Reslizumab	Placebo	United States and Canada	53	53	intravenous	15 weeks	(3.0 mg/kg)	Patients aged 18–75 with asthma was poorly controlled associated with induced sputum eosinophils of 3% or more
Corren J 2016 [18]	Reslizumab	Placebo	United States	77	19	intravenous	16 weeks	(3.0 mg/kg)	Patients aged 18–65 years with asthma inadequately controlled
Bjermer L 2016 [19]	Reslizumab	Placebo	Sweden	106	105	Intravenous	16 weeks	(3.0 mg/kg)	Patients aged 12–75 years with inadequately controlled asthma and had at least one blood eosinophil count of $\geq 400$ cells/ $\mu\text{L}$

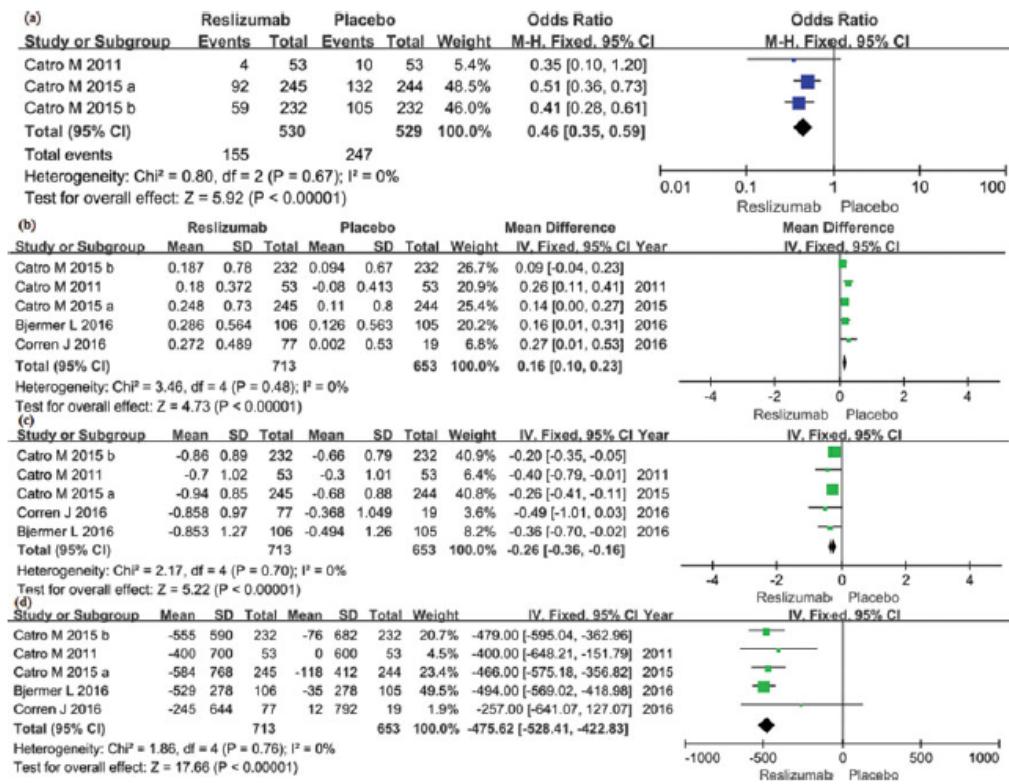
## Qualität der Studien:

**Table 2.** Quality assessment of individual study.

Study	Allocation sequence generation	Allocation concealment	Blinding	Loss to follow-up	Calculation of sample size	Statistical analysis	ITT analysis	Level of quality
Castro M 2015 [16]	A	A	A	7	YES	analysis of covariance	YES	A
Castro M 2011 [17]	A	A	A	0	YES	analysis of covariance	YES	A
Corren J 2016 [18]	A	A	A	1	YES	linear regression analysis	NO	A
Bjermer L 2016 [19]	A	A	A	3	YES	stratified Cochran-Mantel-Haenszel test	NO	A

Note. A - all quality criteria met (adequate): low risk of bias. B - one or more of the quality criteria only partly met (unclear): moderate risk of bias.  
C - one or more criteria not met (inadequate or not used): high risk of bias.

### Studienergebnisse:



**Figure 3.** Forest plots showing changes in (a) asthma exacerbation, (b) FEV<sub>1</sub>, (c) ACQ score and (d) blood eosinophil counts in the treatment studies. FEV<sub>1</sub>: a forced expiratory volume in 1 second; ACQ: Asthma Control Questionnaire; SD: standard deviation, IV: inverse variance; CI: confidence interval, MH: mantel haenszel.

### The proportion of individuals who withdrawn due to AE

- Five RCTs included the proportion of individuals who withdrawn due to AE data representing a cohort of 1365 participants (713 in the reslizumab group and 652 in the placebo group)
- The fixed-effects estimate of the OR was 0.86, and the 95% CI was 0.68 to 1.10 ( $p= 0.24$ ). The result suggests that reslizumab and placebo were similar in terms of the incidence of withdrawn due to AE.

### Upper respiratory AEs

- Five RCTs included the upper respiratory AEs data representing a cohort of 1365 participants (713 in the reslizumab group and 652 in the placebo group).
- The heterogeneity test showed  $P = 0.94$ , so we adopted the fixed-effects model (Figure 4), the OR was 0.67, and the 95% CI was 0.38 to 1.17 ( $p = 0.16$ ).
- The result suggests that reslizumab and placebo were similar in terms of the incidence of upper respiratory AEs.

16. Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, Bardin P, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet Respir Med 2015;3(5):355–66.

17. Castro M, Mathur S, Hargreave F, Boulet LP, Xie F, Young J, et al. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. Am Respir Crit Care Med 2011;184(10):1125–32.

18. Corren J, Weinstein S, Janka L, Zangrilli J, Garin M. Phase 3 Study of reslizumab in patients with poorly controlled asthma: effects across a broad range of eosinophil counts. Chest. in press.

19. Bjermer L, Lemiere C, Maspero J, Weiss S, Zangrilli J, Germinaro M. Reslizumab for inadequately controlled asthma with elevated blood eosinophil levels: A randomized phase 3 study. *Chest*. in press.

### Anmerkung/Fazit der Autoren

This meta-analysis indicates reslizumab to be an effective and safe treatment for eosinophilic asthma.

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### **Cockle SM et al., 2017 [6].**

Comparative effectiveness of mepolizumab and omalizumab in severe asthma: An indirect treatment comparison

### **Fragestellung**

To collect all publicly available RCTs to support an indirect treatment comparison of mepolizumab and omalizumab in severe asthma

### **Methodik**

Bayesian network meta-analysis (Details in Appendix B). A Frequentist network meta-analysis was also conducted.

#### Population:

- 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

#### Intervention:

- mepolizumab and omalizumab

#### Komparator:

- placebo, in addition to SoC

#### Endpunkte:

- 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 (FEV<sub>1</sub>), or postbronchodilator FEV<sub>1</sub>, or FEV<sub>1</sub>% 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

#### Recherche/Suchzeitraum:

- A systematic literature review was conducted on August 5, 2014, and updated on July 8, 2015

## Qualitätsbewertung der Studien:

- Eigene Kriterien in Anlehnung an NICE: Randomisierung angemessen, allocation concealment, Gruppen vergleichbar hinsichtlich prognostisch relevanter Faktoren, Verblindung, Unterschiede bzgl. drop-outs zwischen den Gruppen, selektives Berichten von Endpunkten, ITT-Analyse

## **Ergebnisse**

### Anzahl eingeschlossener Studien:

- The systematic literature review identified seven mepolizumab publications corresponding to three distinct RCTs and 29 omalizumab publications, corresponding to 19 distinct RCTs
- Upon application of the ITC inclusion/exclusion criteria (PICOS), of the 22 identified RCTs, one mepolizumab study (...) and three omalizumab studies (...) were eligible for inclusion in the primary ITC analysis
  - OMA: N=527
  - Mepa: N=1298

### Charakteristika der Population:

**Table 2**  
Key characteristics of double-blind, randomized controlled trials included in the ITC.

Study duration (weeks)	Treatment arms <sup>a</sup>	Key inclusion criteria	Number of patients	Included in Overlap population <sup>b</sup>	Included in Trial population <sup>c</sup> analysis
<b>Mepolizumab-included studies</b>					
MENSA [12] <sup>d</sup>	32	<ul style="list-style-type: none"> <li>• Mepolizumab 100 mg SC every 4 weeks</li> <li>• Placebo (n = 191)</li> </ul>	<ul style="list-style-type: none"> <li>• Blood eosinophil counts <math>\geq 150</math> cells/<math>\mu</math>L at 527 initiation of treatment or <math>\geq 300</math> cells/<math>\mu</math>L in previous 12 months</li> <li>• <math>\geq 2</math> asthma exacerbation in previous 12 months</li> </ul>	✓	✓
<b>Omalizumab-included studies</b>					
INNOVATE [16] <sup>d</sup>	28	<ul style="list-style-type: none"> <li>• Omalizumab administered every 2 or 4 weeks to provide dose of <math>\geq 0.016</math> mg/kg per IU/mL of IgE (n = 209)</li> <li>• Placebo (n = 210)</li> </ul>	<ul style="list-style-type: none"> <li>• Persistent allergic asthma despite high doses of corticosteroids and long-acting <math>\beta_2</math> agonists</li> <li>• <math>\geq 2</math> asthma exacerbation (or 1 severe exacerbation) in previous 12 months</li> </ul>	419	✓ ✓
Chanez et al., 2010 [9] <sup>e</sup>	16	<ul style="list-style-type: none"> <li>• Omalizumab administered every 2 or 4 weeks as per EU prescribing information [9] (n = 20)</li> <li>• Placebo (n = 11)</li> </ul>	<ul style="list-style-type: none"> <li>• Persistent allergic asthma despite high doses of corticosteroids and long-acting <math>\beta_2</math> agonists</li> <li>• <math>\geq 2</math> severe asthma exacerbations in previous 12 months</li> </ul>	31	✓ ✓
EXTRA [18] <sup>f</sup>	48	<ul style="list-style-type: none"> <li>• Omalizumab <math>\geq 0.008</math> mg/kg per IU/mL of IgE every 2 weeks or <math>\geq 0.016</math> mg/kg of IgE every 4 weeks (n = 427)</li> <li>• Placebo (n = 421)</li> </ul>	<ul style="list-style-type: none"> <li>• Severe allergic asthma despite high doses of corticosteroids and long-acting <math>\beta_2</math> agonists</li> <li>• <math>\geq 1</math> asthma exacerbation in previous 12 months</li> </ul>	848	— ✓

IgE, immunoglobulin E; ITC, indirect treatment comparison; SCS, systemic corticosteroids.

<sup>a</sup> For patients included in the base case meta-analysis only.

<sup>b</sup> Including patients potentially eligible for both mepolizumab and omalizumab.

<sup>c</sup> Including all patients eligible for mepolizumab regardless of their eligibility for omalizumab.

<sup>d</sup> Provided data for all efficacy and safety endpoints in the primary Bayesian network meta-analysis of the Overlap and Trial populations.

<sup>e</sup> Provided data for all safety endpoints in the primary Bayesian network meta-analysis of the Overlap and Trial populations.

<sup>f</sup> Provided data for exacerbations and safety endpoints in the primary Bayesian network meta-analysis of the Trial population.

## Qualität der Studien:

- die 4 ausgewerteten RCTs erfüllten fast alle Qualitätskriterien

## **Studienergebnisse:**

- Although asthma control and QoL were pre-specified as efficacy endpoints for the ITC, feasibility assessment demonstrated there was insufficient data in the included studies for endpoint analysis.
- 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

- 59) 9 Genetech. XOLAIR® Summary of Product Characteristics. ; 2009 (accessed May 2016) -  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Product\\_Information/human/000606/WC500057298.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000606/WC500057298.pdf)
- 60) 12 Ortega, H.G., Liu, M.C., Pavord, I.D. et al, Mepolizumab treatment in patients with severe eosinophilic asthma. N. Engl. J. Med. 2014;371:1198–1207.
- 61) 16 Humbert, M., Beasley, R., Ayres, J. et al, Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. Allergy. 2005;60:309–316.
- 62) 18 Hanania, N.A., Alpan, O., Hamilos, D.L. et al, Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial. Ann. Intern. Med. 2011;154:573–582.

### Anmerkung/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.

### Kommentare zum Review

- This study was funded by GlaxoSmithKline, alle Autoren sind Angestellte bei GSK
- 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.

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### Cabon Y et al., 2017 [4].

Comparison of anti-interleukin-5 therapies in patients with severe asthma: global and indirect meta-analyses of randomized placebo controlled trials

### Fragestellung

Inconsistent results have been reported regarding IL-5 blockade treatment in asthma. There were no direct between-treatment comparisons.

### Methodik

- A meta-analysis was first conducted to assess the efficacy of the IL-5 blockade strategy overall

- 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 Brückenkopparator)

Endpunkte:

- annual exacerbation rates, FEV<sub>1</sub> change from baseline and variations in asthma symptoms assessed by changes in the ACQ-5

Recherche/Suchzeitraum:

- from 1990 to September 2015

Qualitätsbewertung der Studien:

- Metaanalyse: Cochrane tool / NMA: R-AMSTAR criteria were assessed to check the overall data quality

## **Ergebnisse**

Anzahl eingeschlossener Studien:

- 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)

Charakteristika der Population:

- The defined exacerbation and population characteristics were quite similar in the eight studies consisting of 10 trials, which involved a total of 3421 patients (59.6% females, average age 47.3 years, average BMI 28.0 kg/ m<sup>2</sup>)

Qualität der Studien:

- 7 RCTs with high quality, 3 RCTs with moderate quality

**Studienergebnisse:**

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.

#### Subgruppenanalyse:

- A specific meta-analysis was performed in the eosinophilic patient subgroup ( $> 300 \text{ mm}^3/\text{L}$ ). For this subgroup, including five studies, the annual exacerbation rate ratio was 0.57 [0.47, 0.69],  $P < 0.01$ ,  $I^2 = 0.54$ . 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] ( $P < 0.01$ ,  $I^2 = 0.21$ ).

#### Netzwerkmetaanalyse:

- Accordingly, the top three treatments with the greatest probability of being ranked first for reducing the exacerbation rate were reslizumab 3 mg/kg with  $P_1 = 51\%$ , followed by mepolizumab 750 mg ( $P_1 = 22\%$ ) and mepolizumab 100 mg ( $P_1 = 13\%$ ).
- 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],  $P_1 = 27\%$ ). Reslizumab 3 mg/kg (0.14 L [0.05, 0.24],  $P_1 = 37\%$ ) 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],  $P_1 = 28\%$ ), 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],  $P_1 = 37\%$ ), again in favour of the treatment.

#### Subgruppenanalyse:

- 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  $P_1 = 41\%$ .
- This treatment was followed by mepolizumab 750 mg with 0.49 [0.23, 1.02] ( $P_1 = 27\%$ ) vs. placebo, and then mepolizumab 100 mg with a 0.54 [0.31, 0.97] ( $P_1 = 11\%$ ) 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],  $P_1 = 29\%$ ) and decreasing the ACQ-5 score (-0.36 [-2.28, 1.56],  $P_1 = 18\%$ ).

- 63) 12 Castro M, Mathur S, Hargreave F et al. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. Am J Respir Crit Care Med 2011; 184:1125–32.
- 64) 13 Castro M, Wenzel SE, Bleeker ERet al. Benralizumab, an anti-interleukin 5 receptor monoclonal antibody versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study. Lancet Respir Med 2014; 2:879–90.
- 65) 15 Castro M, Zangrilli J, Wechsler ME et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet Respir Med 2015; 3:355–66.
- 66) 16 Bel EH, Wenzel SE, Thompson PJ et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. N Engl J Med 2014; 371:1189–97.
- 67) 17 Ortega HG, Liu MC, Pavord ID et al. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med 2014; 371:1198–207.

- 68) 18 Pavord ID, Korn S, Howarth P et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Lancet 2012; 380:651–9.
- 69) 19 Flood-Page P, Swenson C, Faierman I et al. A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma. Am J Respir Crit Care Med 2007; 176:1062–71.
- 70) 20 Haldar P, Brightling CE, Hargadon B et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. N Engl J Med 2009; 360:973–84.

### **Anmerkung/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.

### *Kommentare zum Review*

- Siehe auch: Casale TB et al. [5]

### **Wang FP et al., 2016 [25].**

Efficacy and Safety of Anti-Interleukin- Therapy in Patients with Asthma A Systematic Review and Meta-Analysis

### **Fragestellung**

We conducted a meta-analysis of randomized, controlled trials (RCTs) to assess whether anti-IL-5 monoclonal antibodies therapy is safe and effective in patients (more than 12 years) with asthma.

### **Methodik**

#### Population:

adults/adolescents (12 years) with diagnosis of asthma

#### Intervention:

anti-interleukin-5 monoclonal antibody therapy at any dose

#### Komparator:

placebo-controlled or standard therapy

#### Endpunkte:

Primary outcomes: lung function [first second forced expiratory volume (FEV1), FEV1% of predicted value, peak expiratory flow (PEF), histamine PC<sub>20</sub>], the Asthma Quality of Life Questionnaire (AQLQ) scores, and asthma exacerbation

Secondary outcomes: adverse events and efficacy outcomes [blood eosinophil count, sputum eosinophils (%), short-acting β-agonist (SABA) rescue use].

### Recherche/Suchzeitraum:

PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched for articles published from 1946 to October 2016

### Qualitätsbewertung der Studien:

Cochrane risk of bias

### **Ergebnisse**

#### Anzahl eingeschlossener Studien:

20 RCTs

#### Charakteristika der Population:

Sample sizes ranged from 19 to 1306 subjects.

Nine, five, and six trials used mepolizumab [18-26], reslizumab [27-31], and benralizumab [32-37], respectively.

Treatment duration ranged from 1 day to 56 weeks and follow-up ranged from 12 to 56 weeks.

Nine studies involved patients with severe/refractory asthma [22-28, 36, 37]; four studies included patients with mild, mild to moderate, or moderate asthma [18-21]; the remaining studies did not specify asthma severity [29±35]. Corren et al. [30] and Castro et al. [33] studied patients with noneosinophilic asthma.

#### Qualität der Studien:

Most trials had low risk of bias across the six domains. The allocation sequence was adequately generated and concealed in fourteen trials, [22±29, 32±37]. The randomization techniques included computer generated randomization codes and minimization. The remaining trials did not report the method used, and we were unable to obtain this information. All but one study was described as double-blinded [20]. Almost all RCTs reported complete outcome data, only one trial reported on attrition insufficiently [27].

### Studienergebnisse:

Subgroup analysis of asthma exacerbation and FEV1 in RCTs.

Stratification	asthma exacerbation				FEV <sub>1</sub>			
	No. of Patients (Studies)	RR(95% CI)	P Value	I <sup>2</sup> , %	No. of Patients (Studies)	MD(95% CI)	P Value	I <sup>2</sup> , %
<b>Subgroup analysis</b>								
<b>Effects model</b>								
random-effects model	6072(13)	0.66(0.59–0.73)	<0.001	51	6725(14)	0.09(0.06–0.12)	<0.001	10
fixed effects model	6072(13)	0.63(0.59–0.67)	<0.001	51	6725(14)	0.09(0.06–0.12)	<0.001	10
<b>Asthma severity</b>								
mild or moderate asthma	362(1)	0.85(0.51–1.43)	0.55	...	365(2)	-0.02(-0.2–0.15)	0.8	0
severe asthma	4090(8)	0.59(0.53–0.65)	<0.001	23	3901(7)	0.11(0.07–0.14)	<0.001	35
mixed asthma	1620(4)	0.73(0.65–0.82)	<0.001	18	2459(5)	0.08(0.04–0.12)	<0.001	0

- 71) Studies including patients with severe/refractory asthma  
 72) 22. Haldar P, Brightling CE, Hargadon B, Gupta S, Monteiro W, Sousa A, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. N Engl J Med. 2009; 360(10):973±84. doi: 10.1056/NEJMoa0808991  
 73) 23. Nair P, Pizzichini MMM, Kjarsgaard M, Inman MD, Efthimiadis A, Pizzichini E, et al. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. N Engl J Med. 2009; 360(10):985±93. doi: 10.1056/NEJMoa0805435  
 74) 24. Pavord ID, Korn S, Howarth P, Bleeker ER, Buhl R, Keene ON, et al. Mepolizumab for severe eosinophilic asthma (DREAM): A multicentre, double-blind, placebo-controlled trial. The Lancet. 2012; 380 (9842):651±9. doi: 10.1016/S0140-6736(12)60988-X  
 75) 25. Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, et al. Oral glucocorticoid sparing effect of mepolizumab in eosinophilic asthma. N Engl J Med. 2014; 371(13):1189±97. doi: 10.1056/NEJMoa1403291

- 76) **26.** Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med.* 2014; 371(13):1198±207. doi: 10.1056/NEJMoa1403290 PMID: 25199059.
- 77) **27.** Kips JC, O'Connor BJ, Langley SJ, Woodcock A, Kerstjens HA, Postma DS, et al. Effect of SCH55700, a humanized anti-human interleukin-5 antibody, in severe persistent asthma: a pilot study. *Am J Respir Crit Care Med.* 2003; 167(12):1655±9. Epub 2003/03/22. doi: 10.1164/rccm.200206-525OC PMID: 12649124.
- 78) **28.** Castro M, Mathur S, Hargreave F, Boulet LP, Xie F, Young J, et al. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. *Am J Respir Crit Care Med.* 2011; 184 (10):1125±32. Epub 2011/08/20. doi: 10.1164/rccm.201103-0396OC PMID: 21852542.
- 79) Bleeker ER, FitzGerald JM, Chaney P, Papi A, Weinstein SF, Barker P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dose inhaled corticosteroid Anti-Interleukin-5 Therapy for Asthma and long-acting beta2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet.* 2016. doi: [10.1016/S0140-6736\(16\)31324-1](https://doi.org/10.1016/S0140-6736(16)31324-1) PMID: 27609408.
- 80) **37.** FitzGerald JM, Bleeker ER, Nair P, Korn S, Ohta K, Lommatsch M, et al. Benralizumab, an anti-interleukin-5 receptor alpha monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet.* 2016. doi: [10.1016/S0140-6736\(16\)31322-8](https://doi.org/10.1016/S0140-6736(16)31322-8) PMID: 27609406.

### **Anmerkung/Fazit der Autoren**

Our study indicates that anti-interleukin-5 therapy is safe and may reduce asthma exacerbation risk, slightly improve FEV<sub>1</sub>, FEV1%, and quality of life; and decrease blood and sputum eosinophil levels, although PEF, PC<sub>20</sub> were not improved or SABA rescue use reduced. Antiinterleukin-5 therapy may therefore be beneficial as adjunct asthma therapy, particularly in severe and eosinophilic asthma.

### **Rodrigo GJ et al., 2016 [20].**

Once-daily fluticasone furoate and vilanterol for adolescents and adults with symptomatic asthma. A systematic review with meta-analysis

### **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.

### **Methodik**

#### Population:

- patients with asthma (12 years or older) with documented use of an ICS with or without a LABA

#### Intervention:

- Fluticasone furoate vilanterol

#### Komparator:

- ICS monotherapy or ICS-LABA twice-daily combinations

#### Endpunkte:

- pulmonary function (forced expiratory volume in 1 second [FEV<sub>1</sub>] or peak expiratory flow rate [PEF]) as a primary outcome
- rescue medication use, health status (Asthma Quality of Life Questionnaire [AQLQ] total score), 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,
- 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

#### Recherche/Suchzeitraum:

- bis Januar 2016

#### Qualitätsbewertung der Studien:

- risk of bias assessment according to recommendations outlined in the Cochrane Handbook

Heterogenität: Statistical heterogeneity was measured by the I<sup>2</sup> test (<25% absence, 26%-39% unimportant, 40%-60% moderate, and 60%-100% substantial).

Subgruppen: 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 Chi<sup>2</sup> test from the Peto odds ratios

## Ergebnisse

#### Anzahl eingeschlossener Studien:

- 7 RCTs (N=5.668)

#### Charakteristika der Population:

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

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

#### Qualität der Studien:

- Qualitätsbewertung: the studies had a high methodologic quality

## **Studienergebnisse:**

### 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<sup>27-29</sup>)

- 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<sup>27</sup>)

### Fluticasone FuroateeVilanterol, 100/25 mg, vs Fluticasone Propionatee Salmeterol, 250/50 mg (1 Studie<sup>30</sup>)

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

- 82) [24] Bateman ED, O'Byrne PM, Busse WW, et al. Once-daily fluticasone furoate (FF)/vilanterol reduces risk of severe exacerbations in asthma versus FF alone. Thorax. 2014;69:312e319.  
83) [25] Bernstein DI, Bateman ED, Woodcock A, et al. Fluticasone furoate (FF)/vilanterol (100/25mg or 200/25 mg) or FF (100 mg) in persistent asthma. J Asthma. 2015;52:1073e1083.  
84) [26] Bleeker ER, Lötvall J, O'Byrne PM, et al. Fluticasone furoate-vilanterol 100-25 mg compared with fluticasone furoate 100 mcg in asthma: a randomized trial. J Allergy Clin Immunol Pract. 2014;2:553e561.  
85) [27] Busse WW, O'Byrne PM, Bleeker ER, et al. Safety and tolerability of the novel inhaled corticosteroid fluticasone furoate in combination with the b2 agonist vilanterol administered once daily for 52 weeks in patients 12 years old with asthma: a randomised trial. Thorax. 2013;68:513e520.  
86) [28] Lin J, Kang J, Lee SH, et al. Fluticasone furoate/vilanterol 200/25 mg in Asian asthma patients: a randomized trial. Respir Med. 2015;109:44e53.  
87) [29] O'Byrne PM, Bleeker ER, Bateman ED, et al. Once-daily fluticasone furoate alone or combined with vilanterol in persistent asthma. Eur Respir J. 2014;43:773e782.  
88) [30] Woodcock A, Bleeker ER, Lötvall J, et al. Efficacy and safety of fluticasone furoate/vilanterol compared with fluticasone propionate/salmeterol combination in adult and adolescent patients with persistent asthma: a randomized trial. Chest. 2013;144:1222e1229.

## **Anmerkung/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 furoate-vilanterol, 200/25 µg, and require close and careful monitoring. Future studies should focus on comparison of fluticasone furoate-vilanterol and other combination therapies for safety and efficacy in larger and racially diverse cohorts and studies conducted for a longer duration.

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## Rodrigo GJ et al., 2015 [19].

What Is the Role of Tiotropium in Asthma? A Systematic Review With Meta-analysis.

### Fragestellung

The aim of this systematic review was to assess the efficacy and safety of tiotropium in patients with asthma.

### 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  $\beta$  2 -agonist (LABA)

#### Intervention:

- tiotropium

#### Komparator:

- any treatment

#### Endpunkte:

- primäre Endpunkte: FEV<sub>1</sub> and morning and evening peak expiratory flow (PEF)
- 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), asthma control (Asthma Control Questionnaire 7 [ACQ-7] total score), 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

#### Recherche/Suchzeitraum:

- Medline, Embase, CINAHL, Scopus, and CENTRAL (Cochrane Central Register of Controlled Trials) September 2014

#### Qualitätsbewertung der Studien:

Cochrane Risk of bias tool

- Heterogenität: I<sup>2</sup> test ( $\leq 25\%$ , absent; 26%-39%, unimportant; 40%-60%, moderate; 60%-100%, substantial).

### Ergebnisse

#### Anzahl eingeschlossener Studien:

- 13 RCTs (n=4966)

#### Charakteristika der Population:

- The selected studies were grouped into three treatment protocols:
  - (1) tiotropium OD as add-on to ICS in patients with mild to moderate asthma, 6,18,21-28
  - (2) tiotropium OD added to ICS vs bid LABA plus ICS in patients with moderate asthma, 6,18,26,27
  - (3) tiotropium OD as add-on to LABA plus ICS vs LABA plus ICS in patients with severe asthma. 4,19,20
- Severity was determined according GINA (Global Initiative for Asthma) criteria. 2

- The duration of studies ranged between 4 and 52 weeks.
- Only one study was not sponsored by a pharmaceutical company. 6

Qualität der Studien:

- All but one of the studies showed a low risk of bias in the six items of the Cochrane instrument; the one study had an unclear sequence generation, and concealment was judged to have a high risk of bias.

Studienergebnisse:

- Tiotropium Plus ICS vs LABA Plus ICS (4 Studien)
  - All included patients with moderate asthma
  - Tiotropium significantly improved morning PEF more than LABA, 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<sub>1</sub>
  - 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%).
- Tiotropium as Add-on to LABA Plus ICS (3 Studien)
  - in symptomatic patients with severe asthma
  - Tiotropium as add-on to LABA plus ICS was associated with significant 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 = .15 and P = .68).
  - triple therapy increased peak and trough FEV<sub>1</sub> 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.

TABLE 4 ] Tiotropium as Add-on to ICS Plus LABA vs ICS Plus LABA on Asthma Outcomes (Severe Asthma)

Outcome	Studies <sup>a</sup>	No.	Estimate	Effect (95% CI)	I <sup>2</sup> % (P Value)
FEV <sub>1</sub> peak (change from baseline) L	4, 19, 20 <sup>(1)</sup> , 20 <sup>(2)</sup>	1,169	MD	0.12 (0.09 to 0.16)	26 (.00001)
FEV <sub>1</sub> trough (change from baseline) L	19, 20 <sup>(1)</sup> , 20 <sup>(2)</sup>	1,119	MD	0.08 (0.04 to 0.11)	20 (.00001)
Rescue medication use, puffs/d	20 <sup>(1)</sup> , 20 <sup>(2)</sup>	912	MD	-0.16 (-0.44 to 0.13)	0 (.28)
AQLQ (change from baseline)	4, 19, 20 <sup>(1)</sup> , 20 <sup>(2)</sup>	1,169	MD	0.12 (0.05 to 0.18)	26 (.003)
ACQ-7 (change from baseline)	20 <sup>(1)</sup> , 20 <sup>(2)</sup>	912	MD	-0.20 (-0.25 to -0.09)	73 (.98)
ACQ-7 (responder rate)	20 <sup>(1)</sup> , 20 <sup>(2)</sup>	907	RR	1.29 (1.13 to 1.46)	0 (.0001)
			NNTB	8 (5 to 15)	
No. patients with at least one episode of asthma exacerbation	19, 20 <sup>(1)</sup> , 20 <sup>(2)</sup>	1,119	RR	0.70 (0.53 to 0.94)	0 (.02)
			NNTB	17 (9 to 99)	
Total withdrawals	19, 20 <sup>(1)</sup> , 20 <sup>(2)</sup>	1,119	RR	0.96 (0.64 to 1.44)	22 (.85)
Withdrawals due to worsening asthma	19, 20 <sup>(1)</sup> , 20 <sup>(2)</sup>	1,119	RR	0.55 (0.18 to 1.66)	0 (.29)
Any AE	19, 20 <sup>(1)</sup> , 20 <sup>(2)</sup>	1,119	RR	0.77 (0.59 to 1.01)	15 (.06)
SAE	19, 20 <sup>(1)</sup> , 20 <sup>(2)</sup>	1,119	RR	0.71 (0.32 to 1.55)	55 (.39)

See Table 1-3 legends for expansion of abbreviations.

<sup>a</sup>20<sup>(1)</sup>, 20<sup>(2)</sup> – trials 1 and 2 from Kerstjens et al.<sup>28</sup>

- 89) 4. Fardon T, Haggart K, Lee DKC, Lipworth BJ . A proof of concept study to evaluate stepping down the dose of fluticasone in combination with salmeterol and tiotropium in severe persistent asthma . Respir Med . 2007 ; 101 ( 6 ): 1218 - 1228 .
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- 91) 18 . Bateman ED , Kornmann O , Schmidt P , Pivovarova A , Engel M , Fabbri LM . Tiotropium is noninferior to salmeterol in maintaining improved lung function in B16-Arg/Arg patients with asthma . J Allergy Clin Immunol . 2011 ; 128 ( 2 ): 315 - 322 .
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- 93) 20 . Kerstjens HA , Engel M , Dahl R , et al Tiotropium in asthma poorly controlled with standard combination therapy . N Engl J Med . 2012 ; 367 ( 13 ): 1198 - 1207 .
- 94) 21 . Clinical trials. BI Trial No.: 205.464 Boehringer Ingelheim website. [http://trials.boehringer-ingelheim.com/content/dam/internet/opu/clinicaltrial/com\\_EN/](http://trials.boehringer-ingelheim.com/content/dam/internet/opu/clinicaltrial/com_EN/) results/205/205.464\_U13-2279-01.pdf . Accessed on May 10, 2014.
- 95) 22 . Clinical trials. BI Trial No.: 205.420. Boehringer Ingelheim website. [http://trials.boehringer-ingelheim.com/content/dam/internet/opu/clinicaltrial/\\_com\\_EN/results/205/205.420\\_U12-2227-01-DS.pdf](http://trials.boehringer-ingelheim.com/content/dam/internet/opu/clinicaltrial/_com_EN/results/205/205.420_U12-2227-01-DS.pdf) . Accessed on May 10, 2014.
- 96) 23 . Vogelberg C, Engel M, Moroni-Zentgraf P et al . Tiotropium in asthmatic adolescentssymptomatic despite inhaled corticosteroids:A randomised dose-ranging study .Respir Med . 2014 ; 108 ( 9 ): 1268 - 1276 .24 . Beeh KM, Moroni-Zentgraf P, Ablinger O,et al . Tiotropium Respimat in asthma: adouble-blind, randomised, dose-ranging study in adult patients with moderate asthma . Respir Res . 2014 ; 15 : 61 .
- 97) 25 . Clinical trials. BI Trial No.: 205.442. Boehringer Ingelheim website. [http://trials.boehringer-ingelheim.com/content/dam/internet/opu/clinicaltrial/\\_com\\_EN/results/205/205.442\\_U13-1003-01.pdf](http://trials.boehringer-ingelheim.com/content/dam/internet/opu/clinicaltrial/_com_EN/results/205/205.442_U13-1003-01.pdf) . Accessed on May 10, 2014.
- 98) 26 . Clinical trials. BI Trial No.: 205.418.Boehringer Ingelheim website. [http://trials.boehringer-ingelheim.com/content/dam/internet/opu/clinicaltrial/com\\_EN/\\_results/205/205.418\\_c02036039-03.pdf](http://trials.boehringer-ingelheim.com/content/dam/internet/opu/clinicaltrial/com_EN/_results/205/205.418_c02036039-03.pdf) . Accessed on May 10, 2014.
- 99) 27 . Clinical trials. BI Trial No.: 205.419 Boehringer Ingelheim website. [http://trials.boehringer-ingelheim.com/content/dam/internet/opu/clinicaltrial/com\\_EN/\\_results/205/205.419\\_c02036086-05.pdf](http://trials.boehringer-ingelheim.com/content/dam/internet/opu/clinicaltrial/com_EN/_results/205/205.419_c02036086-05.pdf) .Accessed on May 10, 2014.
- 100) 28 . Clinical trials. BI Trial No.: 205.444.Boehringer Ingelheim website. [http://trials.boehringer-ingelheim.com/content/dam/internet/opu/clinicaltrial/com\\_EN/\\_results/205/205.444\\_c01846621-02.pdf](http://trials.boehringer-ingelheim.com/content/dam/internet/opu/clinicaltrial/com_EN/_results/205/205.444_c01846621-02.pdf) Accessed on September 8, 2014.

### Anmerkung/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

*Kommentare zum Review*

- Patientenpopulation umfasst u.a. Studien mit Patienten ab 12 Jahren
- Beide Autoren haben Interessenkonflikte

## 3.4 Leitlinien

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**Bundesärztekammer (BÄK), 2018 [2].**

Nationale VersorgungsLeitlinie 3. Auflage, 2018 Asthma – Langfassung

### **Leitlinienorganisation/Fragestellung**

die Sicherung der bestmöglichen Lebensqualität und sozialen Teilhabe für Betroffene durch eine individuell optimierte medikamentöse und nicht-medikamentöse Therapie unter Berücksichtigung von Komorbiditäten mit dem Ziel des Erhalts der bestmöglichen Lungenfunktion, der Minimierung von Nebenwirkungen und Langzeitfolgen und der Förderung der Adhärenz

### **Methodik**

#### Grundlage der Leitlinie

Primär werden die Mitgliedsgesellschaften der AWMF, die in den jeweiligen Themenbereichen aktiv sind sowie die Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) angesprochen. Zusätzlich werden Patientenvertreter nach einem festgelegten Verfahren eingeladen. Die Repräsentativität der Leitliniengruppe zur Entwicklung der NVL wird in der Auftaktsitzung durch die Leitlinien-gruppe geprüft.

Die Koordination der NVL-Entwicklung obliegt dem ÄZQ. Jede neue NVL und jede Überarbeitung einer NVL wird bei der AWMF angemeldet.

Die Recherche kann abhängig von der Fragestellung, den vorhandenen Ressourcen und der Evidenzlage auf drei verschiedenen Ebenen (Leitlinien, Aggregierte Evidenz, Primärliteratur) erfolgen.

Die systematische Berücksichtigung der Evidenz zur Formulierung und Graduierung der Empfehlungen orientiert sich an GRADE. Für die endgültige Formulierung und Graduierung von Empfehlungen bei einer Präsenzveranstaltung wurde die Technik des Nominalen Gruppenprozesses

Für die Fälle, in denen Interessenkonflikte durch bezahlte Berater- oder Gutachtertätigkeit, bezahlte Vortragstätigkeit, Geschäftsanteile und Aktien oder Drittmittel durch die Industrie bezüglich eines Themas vorlagen, wurden Enthaltungen beschlossen

#### Recherche/Suchzeitraum:

- Cochrane, Medline
  - Wirksamkeit und Sicherheit von Anti-IL-5-Antikörpern bei Patienten mit Asthma 28.03.2017
  - Wirksamkeit und Sicherheit von Benralizumab 26.04.2018
- Reviews: 26.03. 2016
- Leitlinien: bis 29.01.2016

#### LoE

- Bewertung des Biasrisikos (Risiko systematischer Fehler) in klinischen Studien: ein Manual für die Leitlinienerstellung

## GoR

**Tabelle 1: Einstufung von Leitlinien-Empfehlungen in Empfehlungsgrade (Grades of Recommendation) [8]**

Empfehlungsgrad	Beschreibung	Formulierung	Symbol
A	Starke Positiv-Empfehlung	soll	↑↑
B	Abgeschwächte Positiv-Empfehlung	sollte	↑
0	Offene Empfehlung	kann	↔
B	Abgeschwächte Negativ-Empfehlung	sollte nicht	↓
A	Starke Negativ-Empfehlung	soll nicht	↓↓

## Empfehlungen

### Definition schweres Asthma

Empfehlungen/Statements	Empfehlungsgrad
<p><b>1-1   ERWACHSENE</b></p> <p>Bei Erwachsenen liegt ein schweres Asthma vor, wenn unter Therapie mit inhalativen Corticosteroiden (ICS) in Höchstdosis (siehe Tabelle 6) und mindestens einem zusätzlichen Langzeitmedikament (Langwirkendes Beta-2-Sympathomimetikum oder Montelukast) oder oralen Corticosteroiden (OCS) &gt; 6 Monate/Jahr mindestens einer der folgenden Punkte zutrifft bzw. bei Reduktion der Therapie zutreffen würde:</p> <ul style="list-style-type: none"> <li>• Atemwegsobstruktion: FEV1 &lt; 80% des Sollwertes (FEV1/FVC &lt; LLN);</li> <li>• häufige Exazerbationen: ≥ 2 corticoidsteroidpflichtige Exazerbationen in den letzten 12 Monaten;</li> <li>• schwere Exazerbationen: ≥ 1 Exazerbation mit stationärer Behandlung oder Beatmung in den letzten 12 Monaten;</li> <li>• teilweise kontrolliertes oder unkontrolliertes Asthma (siehe Abbildung 2).</li> </ul>	<b>Statement</b>

## Stufenschema

Medikamentöses Stufenschema   ERWACHSENE					
Langzeittherapie					
	Stufe 1	Stufe 2	Stufe 3	Stufe 4	Stufe 5
		- ICS niedrigdosiert	- ICS niedrigdosiert + LABA (bevorzugt) oder - ICS mitteldosiert	- ICS mittel- bis hochdosiert + LABA (bevorzugt) oder - ICS mittel- bis hochdosiert + LABA + LAMA*	- ICS in Höchstdosis + LABA + LAMA*
Alternativen in begründeten Fällen:					
	- ICS niedrigdosiert	- LTRA	- ICS niedrigdosiert + LAMA* oder - ICS niedrigdosiert + LTRA	- ICS mittel- bis hochdosiert + LABA + LTRA oder - ICS mittel- bis hochdosiert + LAMA*	- OCS (zusätzlich oder alternativ)
Bedarfstherapie	- SABA		- SABA oder - Fixkombination aus ICS und Formoterol, wenn diese auch die Langzeittherapie darstellt		
Asthmaschulung, Allergie-/Umweltkontrolle, Beachtung von Komorbiditäten					
Spezifische Immuntherapie (bei gegebener Indikation)					
Im Stufenschema werden zur besseren Übersicht übergeordnete Arzneimittelkategorien und keine einzelnen Präparate genannt. Nicht alle Präparate und Kombinationen sind für die jeweilige Indikation zugelassen (siehe Fachinformationen), teilweise handelt es sich um einen Off-Label-Use (siehe Kapitel 4 Medikamentöse Therapie).					
* aus der Gruppe der LAMA ist Tiotropium für die Behandlung des Asthmas zugelassen (Stand: September 2018)					
ICS: Inhalative Corticosteroide, IgE: Immunglobulin E, IL-5: Interleukin 5, LABA: Langwirkende Beta-2-Sympathomimetika, LAMA: Langwirkende Anticholinergika, LTRA: Leukotrienrezeptorantagonisten, OCS: Orale Corticosteroide, SABA: Kurzwirkende Beta-2-Sympathomimetika					

## 4.2 Allgemeine Therapieprinzipien innerhalb des Stufenschemas

Empfehlungen/Statements	Empfehlungsgrad
<b>4-3</b> Ein geringer Bedarf an kurzwirkenden Beta-2-Sympathomimetika (SABA) ist ein wichtiges Ziel und ein Kriterium für den Erfolg der Therapie.	<b>Statement</b>
<b>4-4   ERWACHSENE</b> Die Therapie mit inhalativen Corticosteroiden (ICS) soll bei Erwachsenen in den Therapiestufen 2 bis 5 die Basis der Langzeittherapie sein.	↑↑

## Therapieintensivierung

<b>4-10</b>	Bei unkontrolliertem Asthma soll eine Intensivierung der Therapie den Stufenschemata folgend empfohlen werden.	↑↑
<b>4-11</b>	Bei teilweise kontrolliertem Asthma sollte eine Intensivierung der Therapie den Stufenschemata folgend erwogen werden.	↑
<b>4-12</b>	Nach einer Intensivierung der Langzeittherapie gemäß Stufenschema soll die Asthmakontrolle innerhalb von drei Monaten überprüft werden.	↑↑

## Empfehlungen zu Stufe 4

Empfehlungen/Statements	Empfehlungsgrad
<b>4-29   ERWACHSENE</b> Bei Erwachsenen soll in Stufe 4 bevorzugt die Kombination aus einem ICS im mittleren oder hohen Dosisbereich und einem LABA angewandt werden.	↑↑

Eine systematische Übersichtsarbeit [107] verglich die Kombinationstherapie von ICS plus LABA mit einer Dreifachkombination aus ICS, LABA und langwirksamen Anticholinergika (LAMA). Exazerbationen, die mit OCS behandelt werden mussten, traten bei Patienten, die die Dreifachkombination erhielten, seltener auf (271/1 000 vs. 328/1 000). Der Unterschied war jedoch nicht signifikant (OR 0,76 (95% KI 0,57; 1,02);  $I^2 = 1\%$ , 2 RCTs, n = 907, Datenqualität moderat). Ebenfalls nicht signifikant waren die Unterschiede im Gruppenvergleich hinsichtlich der Lebensqualität, der schweren unerwünschten Effekte und der Exazerbationen, die eine Hospitalisierung erforderlich machten. Die Asthmakontrolle, erhoben mit dem Asthma-Control-Questionnaire (ACQ-9), war zugunsten der Dreifachkombination verbessert (MD -0,13 (95% KI -0,23; -0,02);  $I^2 = 0\%$ , 2 RCTs, Datenqualität hoch). Zudem waren jegliche unerwünschten Effekte bei Erhalt der Dreifachkombination seltener (OR 0,70 (95% KI 0,52; 0,94);  $I^2 = 0\%$ , 3 RCTs, n = 1 197, Datenqualität hoch). [107]

Die Autoren sehen eine additive Behandlung mit LAMA zu einer bereits bestehenden Medikation aus ICS in mittlerer oder hoher Dosis plus LABA als Therapiealternative für Patienten mit Asthma in Stufe 4. Wichtig ist, dass in der Stufe 4 alle verfügbaren Therapieoptionen ausgereizt werden, bevor die Therapie zur Stufe 5 eskaliert wird. Dabei entscheidet der Arzt individuell mit dem Patienten (siehe Kapitel 3.1 Gemeinsame Entscheidungsfindung), ob er zunächst die ICS-Dosis erhöht oder zu einer Dreifachkombination übergeht.

### Alternative in begründeten Fällen in Stufe 4 bei Erwachsenen

In begründeten Fällen, insbesondere wenn Kontraindikationen gegen die bisher verwendeten Medikamente vorliegen oder unerwünschte Wirkungen bei deren Anwendung auftreten, empfehlen die Autoren auch die Kombination aus ICS mittel- bis hochdosiert, LABA und LTRA oder ICS mittel- bis hochdosiert und LAMA. In der systematischen Recherche wurden keine Metaanalysen identifiziert, die die Wirksamkeit und Sicherheit der Dreifachkombination evaluierten.

## Empfehlung zu Stufe 5

Empfehlungen/Statements	Empfehlungsgrad
<b>4-32   ERWACHSENE</b> Die Indikation zur Therapie mit monoklonalen Antikörpern sollte erst gestellt werden, wenn selbst unter dreimonatiger maximaler inhalativer antioberstruktiver Kombinationstherapie mit einem ICS in Höchstdosis, einem LABA und einem LAMA (Tiotropium) keine Asthmakontrolle erreicht wird.	↑

Darüber hinaus weist die Leitliniengruppe darauf hin, dass die Therapie mit monoklonalen Antikörpern in Stufe 5 sehr aufwändig und über einen längeren Zeitraum mit hohen Kosten verbunden ist. Vor diesem Hintergrund erachten sie es

als notwendig, dass die in der Empfehlung 4-32 genannte Dreifachkombination mit ICS hochstdo-siert (siehe Tabelle 6) über drei Monate evaluiert wird, bevor die Therapie mit monoklonalen Antikörpern initiiert wird. Der Eindruck aus der Versorgungssituation ist, dass die Kombination ICS plus LABA plus LAMA vor einer weiteren Therapieeskalation häufig nicht ausgeschöpft wird, da es sich um ein eher neueres Therapiekonzept handelt.

Empfehlungen/Statements	Empfehlungsgrad
<p><b>4-33   ERWACHSENE</b></p> <p>Ein Therapieversuch mit Omalizumab für mindestens vier Monate soll bei Erwachsenen in Stufe 5 empfohlen werden, wenn folgende Kriterien vorliegen:</p> <ul style="list-style-type: none"> <li>• schweres IgE-vermitteltes allergisches Asthma und</li> <li>• positiver Hauttest oder in-vitro Reaktivität gegen ein ganzjährig auftretendes Aeroallergen und</li> <li>• IgE-Serumkonzentration unter Berücksichtigung des Körpergewichts im therapierten Bereich und</li> <li>• erfolgte Eliminierung vermeidbarer Allergenexpositionen.</li> </ul>	↑↑

Im Cochrane-Review von Normansell et al. [115] senkte Omalizumab während der kontinuierlichen Corticostero-idgebe das Risiko für eine oder mehr Exazerbationen im Vergleich zu Placebo (OR 0,55 (95% KI 0,46; 0,65);  $I^2 = 50\%$ , 10 RCTs, n = 3 261, moderate Datenqualität) und die Häufigkeit von Hospitalisierungen (OR 0,16 (95% KI 0,06; 0,42);  $I^2 = 0\%$ , 4 RCTs, n = 1 824, moderate Datenqualität). Bei schwererer Erkrankung war der Effekt von Omalizumab hinsichtlich der Exazerbationen nicht mehr signifikant [115].

Die Daten zur Sicherheit wurden für die steroidstabile und die Ausschleichphase gemeinsam ausgewertet [115]. Schwere unerwünschte Wirkungen waren in der Gruppe der mit Omalizumab behandelten Patienten weniger wahrscheinlich (OR 0,72 (95% KI 0,57; 0,91);  $I^2 = 7\%$ , 15 RCTs, n = 5 713, Datenqualität moderat). Hinsichtlich jeglicher unerwünschter Wirkungen und Mortalität ergab sich kein Unterschied. Reaktionen an der Injektionsstelle waren unter Omalizumab höher (OR 1,72 (95% KI 1,33; 2,24);  $I^2 = 42\%$ ; 9 RCTs, n = 3 577, Datenqualität mode-rat). [115]

Die gepoolten Auswertungen von Daten aus Studien mit einer Dauer von 52 bis 60 Wochen von Lai et al. zeigten ähnliche Tendenzen für die oben genannten Endpunkte [118].

Empfehlungen/Statements	Empfehlungsgrad
<p><b>4-34   ERWACHSENE</b></p> <p>Ein Therapieversuch mit Mepolizumab, Reslizumab oder Benralizumab für mindestens vier Monate sollte bei Erwachsenen in Stufe 5 erwogen werden, wenn folgende Kriterien vorliegen:</p> <ul style="list-style-type: none"> <li>• schweres eosinophiles Asthma und</li> <li>• zweimaliger Nachweis einer Konzentration von &gt; 300 Eosinophilen pro <math>\mu\text{l}</math> Blut außerhalb von Exazerbationen in den vergangenen zwei Jahren.</li> </ul>	↑

Im Vergleich zu Placebo senkte die subkutanen Gabe von Mepolizumab in einem Studienzeitraum von 32 Wochen (MENSA) die Rate klinisch relevanter Exazerbationen (0,83 vs. 1,74; Rate Ratio 0,47 (95% KI 0,35; 0,63); 1 RCT, n = 385, Datenqualität moderat) und die Anzahl der Exazerbationen, die das Aufsuchen einer Notaufnahme oder eine Hospitalisierung nach sich zogen [122]. Des Weiteren verbesserten sich die Lebensqualität und die Symptome signifikant, letztere allerdings nicht klinisch relevant [122].

Ein RCT (SIRIUS) [123] mit 135 Teilnehmern berichtet, dass durch die subkutane Applikation von Mepolizumab über einen Zeitraum von 24 Wochen im Vergleich zu Placebo mehr OCS eingespart werden konnten (OR 2,39 (95% KI 1,25; 4,56)). Auch die jährlich Exazerbationsrate verbesserte sich durch Mepolizumab trotz der OCS-Reduktion (Rate Ratio 0,68 (95% KI 0,47; 0,99)) [123]. Die niedrige Fallzahl und die fehlende Verblindung der Ergebnisevaluation stellen allerdings ein Risiko für eine Verzerrung dar.

Die Phase-III-Studie von Corren et al. [125] prüfte die Abhängigkeit der Wirksamkeit und Sicherheit von Reslizumab von der Eosinophilenzahl im Blut bei Patienten der Altersgruppe von 18 bis 65 Jahren über einen Zeitraum von 16 Wochen. Bei der Ausgangserhebung wiesen 20% der eingeschlossenen Patienten eine Eosinophilenzahl  $\geq 400/\mu\text{l}$  auf. Eine klinisch relevante Verbesserung der Asthmakontrolle, gemessen mit dem ACQ-7, war unter Reslizumab häufiger als in der Placebogruppe. Je höher die Eosinophilenzahl war, desto deutlicher war die Verbesserung der Asthmakontrolle. Die Fallzahl für diese Subgruppenanalyse war jedoch gering und die Power der Studie genügte nicht, um repräsentative Ergebnisse zu generieren. [125]

Gestützt werden die Aussagen von Corren et al. [125] durch eine weitere Phase-III-Studie [126], bei der eine mindestens einmalige Erhöhung der Eosinophilenzahl auf  $\geq 400/\mu\text{l}$  eines der Einschlusskriterien war. Untersucht wurden die

Dosierungen 0,3 mg/kg Körpergewicht (KG) und 3,0 mg/kg KG im Vergleich zu Placebo. Sowohl die Asthmasymptome als auch die Asthmakontrolle, erhoben mit dem ACQ, verbesserten sich in beiden Interventionsgruppen im Vergleich zu Placebo. Die Verbesserung der Lebensqualität, gemessen mit dem AQLQ, wurde nur bei der höheren Dosierung ersichtlich, war jedoch klinisch nicht relevant (delta of least square mean 0,359 (95% KI 0,047; 0,670). [126] Die Qualität der Studie ist durch ein unklares Risiko für Selektionsbias, Performance bias, Detection bias und ein hohes Risiko für Attrition bias limitiert.

Die subkutane Anwendung von Benralizumab bei schwerem Asthma wurde in zwei Phase-III-Studien (SIROCCO und CALIMA) untersucht, die sehr ähnliche Studiendesigns, jedoch leicht differierende Beobachtungszeiträume hatten [127,128]. In der Studie CALIMA führte die subcutane Gabe von Benralizumab im 4-Wochen-Intervall (Rate Ratio 0,64 (95% KI 0,49; 0,85) und im 8-Wochen-Intervall (Rate Ratio 0,72 (95% KI 0,54; 0,95)) über einen Zeitraum von 56 Wochen im Vergleich zu Placebo zur Reduktion der jährlichen Exazerbationsrate [127]. In der Studie SIROCCO führte die subcutane Gabe von Benralizumab im 4-Wochen-Intervall (Rate Ratio 0,55 (95% KI 0,42; 0,71) und im 8-Wochen-Intervall (Rate Ratio 0,49 (95% KI 0,37; 0,64)) über einen Zeitraum von 48 Wochen im Vergleich zu Placebo zur Reduktion der jährlichen Exazerbationsrate [128]. Die Asthmasymptome verbesserten sich im Vergleich zu Placebo in beiden Studien nur in der Gruppe der im 8-Wochen-Intervall behandelten Patienten [127,128]. Unklar bleibt, ob die Ergebnisevaluation in den Studien ver-blindet erfolgte.

Eine weitere Phase-III-Studien (BISE) untersuchte die Wirksamkeit und Sicherheit von Benralizumab im Vergleich zu Placebo bei Patienten mit mildem bis moderatem Asthma: Hier ergaben sich hinsichtlich des Symptomscores und der asthmabezogenen Lebensqualität keine signifikanten Unterschiede zwischen der Interventions- und der Placebogruppe [129].

Überdies untersuchte die Studie ZONDA [130] den corticosteroidsparenden Effekt von Benralizumab über einen Zeitraum von 28 Wochen. Die Chance einer Reduktion von OCS war bei der Gabe von Benralizumab im 4-Wochen-Intervall OR 4,09 (95% KI 2,22; 7,57) und im 8-Wochen-Intervall OR 4,12 (95% KI 0,22; 7,63) höher als bei der Gabe von Placebo [130].

Ein Wirksamkeitsvergleich zwischen den einzelnen monoklonalen Antikörpern wurde in der systematischen Recherche nicht identifiziert.

Zu Sicherheitsaspekten von Mepolizumab, Reslizumab und Benralizumab stehen bisher nur die Zulassungsstudien bzw. teilweise deren Verlängerungen zur Verfügung. In einigen Studien floss der nicht näher bzw. ungenau definierte Endpunkt „Verschlechterung des Asthmas“ als unerwünschte Wirkung ein: Hier blieb meist unklar, ob zum Beispiel auch die Effektivitätsendpunkte Exazerbationen oder Symptome mit ausgewertet wurden [123–126]. Teilweise wurde in den identifizierten Studien ersichtlich, dass es sich dabei auch um Exazerbationen handelt [127–130,139]. Vor diesem Hintergrund lassen sich ähnliche oder erhöhte Raten an unerwünschten und schweren unerwünschten Nebenwirkungen in der Placebogruppe erklären [122–130].

Empfehlungen/Statements	Empfehlungsgrad
<p><b>4-38   ERWACHSENE</b></p> <p>Die Langzeittherapie mit systemischen Corticosteroiden soll bei Erwachsenen in Stufe 5 wegen der Gefahr schwerer Nebenwirkungen nicht empfohlen werden, es sei denn, die Asthmakontrolle ist trotz des kombinierten Einsatzes der verschiedenen Therapieoptionen der vorherigen Stufe sowie zusätzlich monoklonaler Antikörper (sofern indiziert und wirksam) unzureichend.</p>	↓↓

Auch wenn zum aktuellen Zeitpunkt nur begrenzte Langzeiterhebungen für die Sicherheit der verschiedenen monoklonalen Antikörper vorliegen (siehe Empfehlungen 4-33, 4-34 bis 4-37), werden die unerwünschten Langzeitwirkungen von systemischen Corticosteroiden als so erheblich eingeschätzt, dass die Leitliniengruppe OCS als nachrangige Therapieoption für die Langzeittherapie in Stufe 5 einordnen.

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## National Institute for Health and Care Excellence (NICE), 2017 [18].

Asthma: diagnosis, monitoring and chronic asthma management.

### Leitlinienorganisation/Fragestellung

NICE has produced guidance on the components of good patient experience in adult NHS services.

### Methodik

#### Grundlage der Leitlinie

This guideline will contain recommendations for the management of symptoms in adults, young people and children who have been diagnosed with asthma. Specific consideration will be given to subgroups based on age: children under 5 years; children aged 5–16 years; and adults and young people over 16 years of age.

Update: Following publication, and in accordance with the NICE guidelines manual, NICE will undertake a review of whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update.

#### Recherche/Suchzeitraum:

- 09/2016

#### LoE/GoR

#### Overall quality of outcome evidence in GRADE

Level	Description
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	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	Any estimate of effect is very uncertain

### Empfehlungen

#### Treatment in patients not on regular preventers

*Review question: What is the clinical and cost effectiveness of using ICS + LABA as preventer and reliever therapy compared to using ICS + LABA as preventer and a SABA as reliever therapy?*

20. If asthma is uncontrolled in adults (aged 17 and over) on a low dose of ICS and a LABA, with or without an LTRA, as maintenance therapy, offer to change the person's ICS and LABA maintenance therapy to a MART regimen with a low maintenance ICS dose.

21. If asthma is uncontrolled in adults (aged 17 and over) on a MART regimen with a low maintenance ICS dose, with or without an LTRA, consider increasing the ICS to a moderate maintenance dose (either continuing on a MART regimen or changing to a fixed-dose of an ICS and a LABA, with a SABA as a reliever therapy).

22. If asthma is uncontrolled in children and young people (aged 5 to 16) on a paediatric low dose of ICS and a LABA as maintenance therapy, consider changing their ICS and LABA

maintenance therapy to a MART regimen<sup>10</sup> with a paediatric low maintenance ICS dose. Ensure that the child or young person is able to understand and comply with the MART regimen.

23. If asthma is uncontrolled in children and young people (aged 5 to 16) on a MART regimen<sup>11</sup> with a paediatric low maintenance ICS dose, consider increasing the ICS to a paediatric moderate maintenance dose (either continuing on a MART regimen or changing to a fixed-dose of an ICS and a LABA, with a SABA as a reliever therapy).

Quality of the clinical evidence:

The quality of the evidence ranged from High to Very Low quality. The majority of the evidence was either Moderate or High quality.

There was limited evidence regarding the total steroid dose, with only one study, one of the smaller studies, reporting this particular outcome.

The committee noted that 2 of the studies<sup>163,185</sup> compared MART versus ICS + LABA as maintenance and SABA as reliever where the doses were in the same category (i.e. low dose ICS + LABA) but there were differences in precise dosing or within class drug choice. The conclusions of these studies were similar to the overall body of evidence.

*Review question: What is the most clinically and cost-effective drug (class or combination of drug classes) for the management of children, young people and adults with asthma who are currently taking optimal preventer therapy beyond ICS low dose when this fails to provide adequate control?*

24. If asthma is uncontrolled in adults (aged 17 and over) on a moderate maintenance ICS dose with a LABA (either as MART or a fixed dose regimen) with or without an LTRA, consider:

- increasing the ICS to a high maintenance dose (this should only be offered as part of a fixed-dose regimen, with a SABA used as a reliever therapy) or
- a trial of an additional drug (for example, a long-acting muscarinic receptor antagonist or theophylline) or
- seeking advice from a healthcare professional with expertise in asthma.

Quality of the clinical evidence:

The quality of the evidence for this review ranged from Very Low to High quality. The majority of the evidence was either Low or Moderate quality. Most of the studies compared adding a new agent or increasing ICS dose against continuing on previous treatment with or without a placebo. The majority of the evidence was in people uncontrolled on ICS moderate dose. None of the evidence addressed the addition of treatment in people uncontrolled on ICS and LTRA.

Studies were found in which the baseline population were on treatment not recommended by the committee in this guideline. This included studies in people who were using a high or moderate dose ICS (without first adding in a LABA or LTRA). The committee included this population as it represents a group who are uncontrolled despite preventer treatment beyond the first line of low dose ICS, and because there will be patients currently on this treatment.

Trade-off between clinical benefits and harms

Uncontrolled on ICS moderate dose, adults

Possible interventions identified in the evidence at this stage included the addition of a LABA, addition of a LABA and conversion to MART, increasing ICS dose, addition of an LTRA, addition of a LAMA and addition of a theophylline. Any one of the additional preventers could be accompanied by an increase or decrease in steroid dose simultaneously.

Consistent with the review of interventions for those uncontrolled on ICS low dose, the addition of a LABA appeared to have the greatest benefit for critical outcomes like severe exacerbations. Again consistent with the previous review there was little difference between addition of a LABA and addition of an LTRA when compared directly, although the addition of an LTRA had less benefit than addition of a LABA when compared to continuing on ICS moderate dose. Consistent with the evidence in the population uncontrolled on ICS + LABA, the use of MART appeared to have clinically important benefits over ICS + LABA + SABA when required.

Uncontrolled on ICS high dose, adults

Possible interventions identified in the evidence at this stage included the addition of a LABA, addition of a LABA and conversion to MART and addition of an LTRA. Any one of the additional preventers could be accompanied by a change in steroid dose.

There was evidence of a clinically important benefit of addition of LABA compared to continuation on ICS high dose in terms of reliever medication use. The direct comparison between addition of LABA and conversion to MART as opposed to just addition of LABA showed a clinically important benefit for MART in terms of severe exacerbations

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### **Global Initiative for Asthma (GINA), 2019 [13].**

*GINA – Global Initiative for Asthma*

Global strategy for asthma management and prevention; updated 2019.

#### **Methodik**

##### Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

#### **LITERATURE REVIEWED FOR GINA 2019 UPDATE**

The GINA report has been updated in 2019 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 1137 publications, of which 906 were screened out for duplicates, relevance and/or quality. The remaining 231 publications (149 'clinical trials' and 82 meta-analyses) were reviewed by at least two members of the Science Committee; 123 were subsequently discussed at face-to-face meetings in May 2018 in San Diego, USA and in September 2018 in Paris, France. A list of key changes in GINA 2019 can be found starting on p.12, and a tracked changes copy of the 2018 report is archived on the GINA website.

#### LoE : 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 undertaken 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

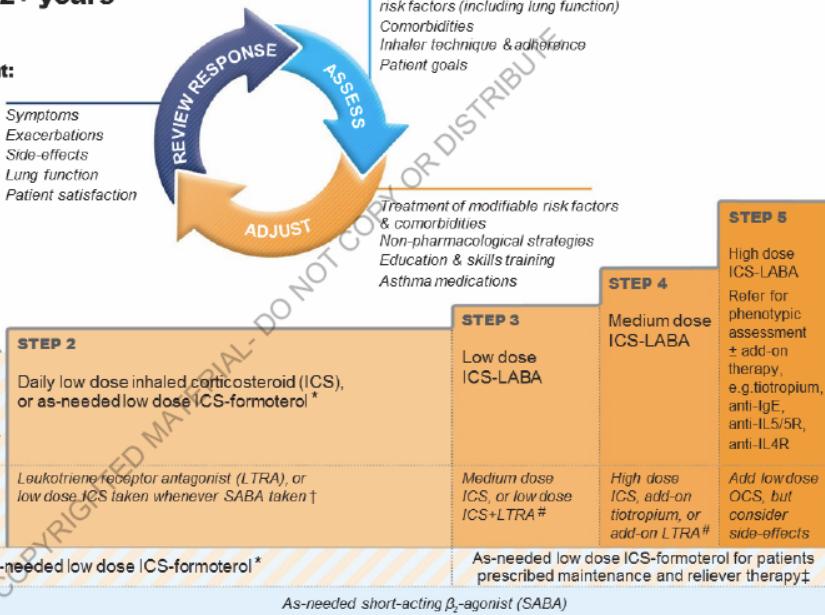
- keine Angabe des GoR.

## Empfehlungen

### Adults & adolescents 12+ years

#### Personalized asthma management:

Assess, Adjust, Review response



\* Off-label; data only with budesonide-formoterol (bud-form)  
 † Off-label; separate or combination ICS and SABA inhalers

‡ Low-dose ICS-form is the reliever for patients prescribed bud-form or BDP-form maintenance and reliever therapy

# Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV1 >70% predicted

**STEP 3: Preferred controller options: Low dose ICS-LABA maintenance plus as-needed SABA, OR low dose ICS-formoterol maintenance and reliever therapy (adults and adolescents); medium dose ICS plus as-needed SABA OR low-dose combination ICS-LABA plus as-needed SABA (children 6-11 years)**

Before considering a step 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).

#### Preferred Step 3 controller options for adults and adolescents

For adults and adolescents, there are two 'preferred' Step 3 options: combination low dose ICS-LABA as maintenance treatment with as-needed SABA as reliever, and low dose ICS-formoterol as both maintenance and reliever treatment. For patients receiving maintenance ICS treatment with as-needed SABA, adding LABA in a combination inhaler provides additional improvements in symptoms and lung function with a reduced risk of exacerbations compared with the same dose of ICS,<sup>198-200</sup> (Evidence A) but there is only a small reduction in reliever use.<sup>199,200</sup> Currently approved

combination ICS-LABA inhalers for Step 3 maintenance treatment of asthma include low doses of fluticasone propionate-formoterol, fluticasone furoate-vilanterol, fluticasone propionate-salmeterol, beclometasone-formoterol, budesonide-formoterol and mometasone-formoterol (see Box 3-6, p.48). Effectiveness of fluticasone furoate-vilanterol over usual care was demonstrated for asthma symptom control in a large real-world study, but there was no difference in exacerbations.<sup>68,201</sup>

The ICS-formoterol maintenance and reliever regimen can be prescribed with low dose beclometasone-formoterol or budesonide-formoterol. In adult and adolescent patients with  $\geq 1$  exacerbation in the previous year, the ICS-formoterol maintenance and reliever regimen significantly reduces exacerbations and provides similar levels of asthma control at relatively low doses of ICS, compared with a fixed dose of ICS-LABA as maintenance treatment or a higher dose of ICS, both with as-needed SABA<sup>202-207</sup> (Evidence A). Low dose ICS-formoterol is the preferred reliever for patients prescribed the maintenance and reliever treatment regimen. It should not be used as the reliever for patients taking combination ICS-LABA medications with a different LABA.

#### *Other Step 3 controller options for adults and adolescents*

For adult patients with allergic rhinitis and sensitized to house dust mite, with suboptimally controlled asthma despite low to high dose ICS, consider adding sublingual allergen immunotherapy (SLIT), provided FEV<sub>1</sub> is  $>70\%$  predicted.<sup>208,209</sup> (see p.58).

Another option for adults and adolescents is to increase ICS to medium dose (see Box 3-6, p.48), but at a group level this is less effective than adding a LABA<sup>128,210,211</sup> (Evidence A). Other less efficacious options are low dose ICS plus either LTRA<sup>212</sup> (Evidence A) or low dose, sustained-release theophylline<sup>213</sup> (Evidence B).

#### *Step 3 controller options for children 6-11 years*

In children, after checking inhaler technique and adherence, and treating modifiable risk factors, the preferred options at a population level are to increase ICS to medium dose (see Box 3-6, p.48), (Evidence A)<sup>214</sup> or change to combination low dose ICS-LABA (Evidence A).<sup>215</sup> In a large study of children aged 4-11 years with a history of an exacerbation in the previous year, combination ICS-LABA was non-inferior to the same dose of ICS alone for severe exacerbations, with no difference in symptom control or reliever use.<sup>216</sup> There has been one study of maintenance and reliever therapy with low dose budesonide-formoterol in children; it showed a large reduction in exacerbations compared with the same dose of budesonide-formoterol with SABA reliever, or compared with higher dose ICS.<sup>217</sup> This regimen is not approved for children  $<12$  years.

### **STEP 4: Preferred controller: Low dose ICS-formoterol as maintenance and reliever therapy (adults and adolescents), OR medium dose ICS-LABA maintenance plus as-needed SABA (adults, adolescents and children).**

Although at a group level most benefit from ICS is obtained at low dose, individual ICS responsiveness varies, and some patients whose asthma is uncontrolled on low dose ICS-LABA despite good adherence and correct technique may benefit from increasing the maintenance dose to medium. High dose ICS is no longer recommended at Step 4.

#### *Preferred Step 4 controller options for adults and adolescents*

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, p.36).

For adult and adolescent patients with  $\geq 1$  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<sup>208</sup> (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 to medium 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<sup>158</sup> (Evidence B); combination ICS-LABA medications are as for Step 3.

#### *Other Step 4 controller options for adults and adolescents*

Tiotropium (long-acting muscarinic antagonist) by mist inhaler may be used as add-on therapy in patients aged 6 years and older; it modestly improves lung function<sup>218,219</sup> (Evidence A) and modestly reduces exacerbations.<sup>218-220</sup> In Step 4, there is insufficient evidence to support ICS+tiotropium over ICS-LABA combination.<sup>220</sup>

For adult patients with allergic rhinitis and sensitization to house dust mite, with suboptimally controlled asthma despite low-high dose ICS, consider adding sublingual allergen immunotherapy (SLIT), provided FEV<sub>1</sub> is >70% predicted.<sup>208,209</sup> (see p.58).

Theophylline should not be used in children. For medium or high dose budesonide, efficacy may be improved with dosing four times daily<sup>221,222</sup> (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<sup>223-227</sup> (Evidence A), or low dose sustained-release theophylline<sup>193</sup> (Evidence B).

#### *Step 4 options for children 6-11 years*

For children 6–11 years, if asthma is not well controlled on moderate dose ICS (see Box 3-6, p.48), the recommendation is to refer the child for expert assessment and advice.

Tiotropium (long-acting muscarinic antagonist) by mist inhaler may be used as add-on therapy in children aged 6 years and older; it modestly improves lung function and reduces exacerbations<sup>218</sup> (Evidence A).

#### **STEP 5: Preferred option: Refer for phenotypic assessment 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 investigation and management of severe asthma<sup>138</sup> (Evidence D).

The GINA Pocket Guide and decision tree on Diagnosis and Management of difficult-to-treat and severe asthma in adolescent and adult patients are included in Chapter 3E (p.84). Treatment options that may be considered after optimization of existing therapy may include the following. **Always check local eligibility and payer criteria.**

- **Combination high dose ICS-LABA:** this may be considered in adults and adolescents, but the increase in ICS dose generally provides little additional benefit<sup>120,128,211,228</sup> (Evidence A), and there is an increased risk of side-effects, including adrenal suppression.<sup>229</sup> 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<sup>193,228</sup> Evidence B).
- **Add-on tiotropium** (long-acting muscarinic antagonist) in patients aged ≥6 years whose asthma is not well-controlled with ICS-LABA. Add-on tiotropium (mostly 5µg once daily by mist inhaler) modestly improves lung function (Evidence A) and modestly increases the time to severe exacerbation requiring oral corticosteroids (Evidence B).<sup>219,220</sup> There is no evidence with other LAMA preparations.<sup>219</sup>
- **Add-on azithromycin** (three times a week, off-label) for adult patients with persistent symptomatic asthma despite moderate-high dose ICS and LABA reduced asthma exacerbations in eosinophilic<sup>230</sup> and non-eosinophilic asthma<sup>230,231</sup> (Evidence B) and improved asthma-related quality of life<sup>230,231</sup> (Evidence B). Diarrhea was more common.<sup>230</sup> Since macrolides such as azithromycin can cause ototoxicity and cardiac arrhythmia, asthma patients with hearing impairment<sup>230</sup> or abnormal prolongation of the corrected QT interval<sup>230,231</sup> were excluded from the studies. Before considering add-on off-label therapy with azithromycin in adult patients with uncontrolled or severe asthma, sputum should be checked for atypical mycobacteria, and the risk of increasing antimicrobial resistance at the patient and the population level should be taken into account.
- **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 4-5 treatment<sup>232,233</sup> (Evidence A).

- **Add-on anti-interleukin-5/5R treatment** (subcutaneous mepolizumab for patients aged  $\geq 12$  years; intravenous reslizumab for ages  $\geq 18$  years) or anti-interleukin 5 receptor treatment (subcutaneous benralizumab for ages  $\geq 12$  years), with severe eosinophilic asthma that is uncontrolled on Step 4-5 treatment (Evidence A).<sup>234-238</sup>
- **Add-on anti-interleukin-4R  $\alpha$  treatment** (subcutaneous dupilumab) for patients aged  $\geq 12$  years with severe Type 2 asthma, or requiring treatment with maintenance OCS (Evidence A).<sup>239,240</sup>
- **Sputum-guided treatment:** for adults 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<sup>158</sup> (Evidence A).
- **Add-on treatment with bronchial thermoplasty:** may be considered for some adult patients with severe asthma<sup>136,241</sup> (Evidence B). Evidence is limited and in selected patients (see p.59). The long term effects compared with control patients, including for lung function, are not known.
- **Add-on low dose oral corticosteroids** ( $\leq 7.5$  mg/day prednisone equivalent): may be effective for some adults with severe asthma<sup>136</sup> (Evidence D), but are often associated with substantial side effects<sup>242,243</sup> (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 and other add-on treatments. Patients should be counseled about potential side-effects (Evidence D).<sup>243</sup> They should be assessed and monitored for risk of corticosteroid-induced osteoporosis, and those expected to be treated for  $\geq 3$  months should be provided with relevant lifestyle counselling and prescription of therapy for prevention of osteoporosis (where appropriate).<sup>244</sup>

#### **Stepping up asthma treatment**

Asthma is a variable condition, and periodic treatment adjustments by the clinician and/or the patient may be needed.<sup>249</sup>

- *Sustained step up (for at least 2–3 months):* although at a group level most benefit from ICS is obtained at low dose, individual ICS responsiveness varies, and some patients whose asthma is uncontrolled on low dose ICS-LABA despite good adherence and correct technique may benefit from increasing the maintenance dose to medium. 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.

## PART E. DIFFICULT-TO-TREAT AND SEVERE ASTHMA IN ADULTS AND ADOLESCENTS

### KEY POINTS

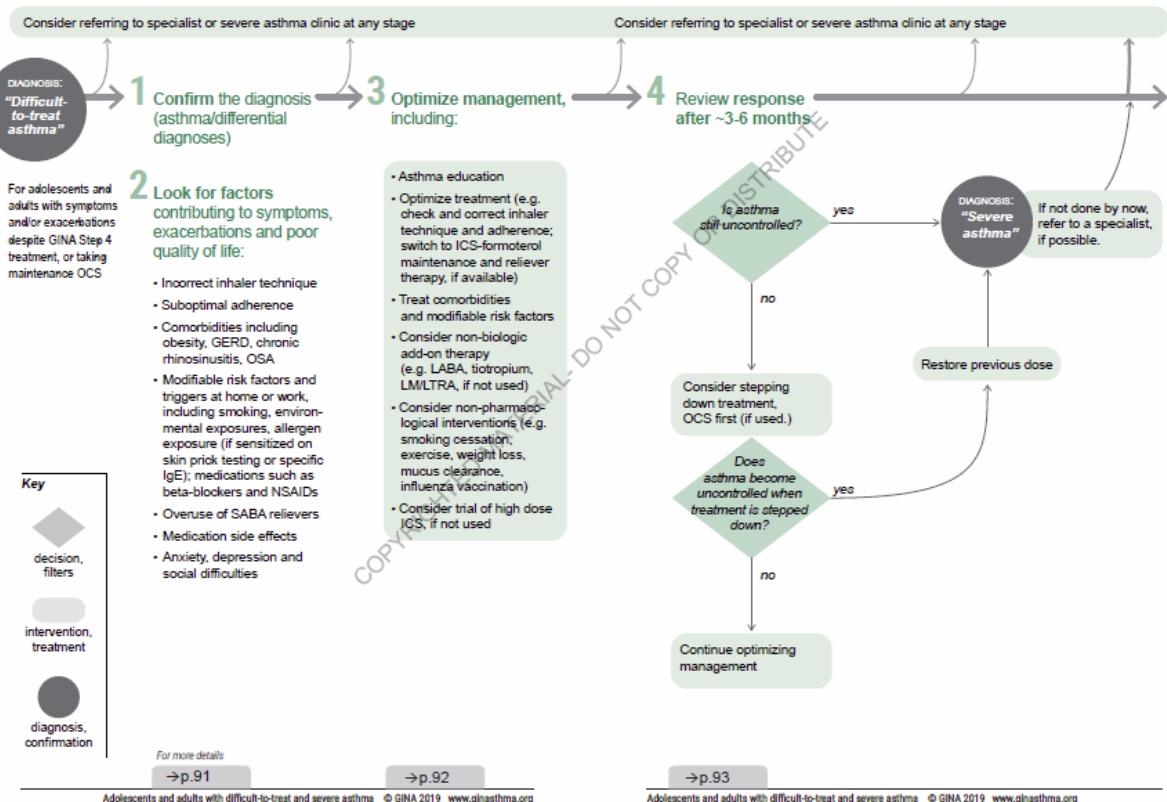
- Difficult-to-treat asthma is asthma that is uncontrolled despite GINA Step 4 or 5 treatment or that requires such treatment to maintain good symptom control and reduce exacerbations. It does not mean a 'difficult patient'.
- Severe asthma is asthma that is uncontrolled despite adherence with maximal optimized Step 4 or Step 5 therapy and treatment of contributory factors, or that worsens when high dose treatment is decreased. Approximately 3-10% of people with asthma have severe asthma.
- Severe asthma places a large physical, mental, emotional, social and economic burden on patients
- Assess all patients with difficult to treat asthma to confirm the diagnosis of asthma, and to identify and manage factors that may be contributing to symptoms, poor quality of life, or exacerbations. Refer for expert advice at any stage, or if asthma does not improve in response to optimizing treatment.
- For patients with persistent symptoms and/or exacerbations despite high dose ICS, the clinical or inflammatory phenotype should be assessed, as this may guide the selection of add-on treatment
- Add-on treatments for severe asthma include tiotropium, LTRA and low dose macrolides, and biologic agents for severe allergic or severe Type 2 asthma. Maintenance OCS should be avoided if other options are available, because of its serious side-effects
- Assess the response to any add-on treatment, stop ineffective treatments, and consider other options
- Utilize multidisciplinary team care for severe asthma, if available
- For patients with severe asthma, continue to optimize patient care in collaboration with the primary care clinician, and taking into account the patient's social and emotional needs
- Invite patients with severe asthma to enrol in a registry or clinical trial, if available and relevant, to help fill evidence gaps

Severe asthma decision tree: diagnosis and management

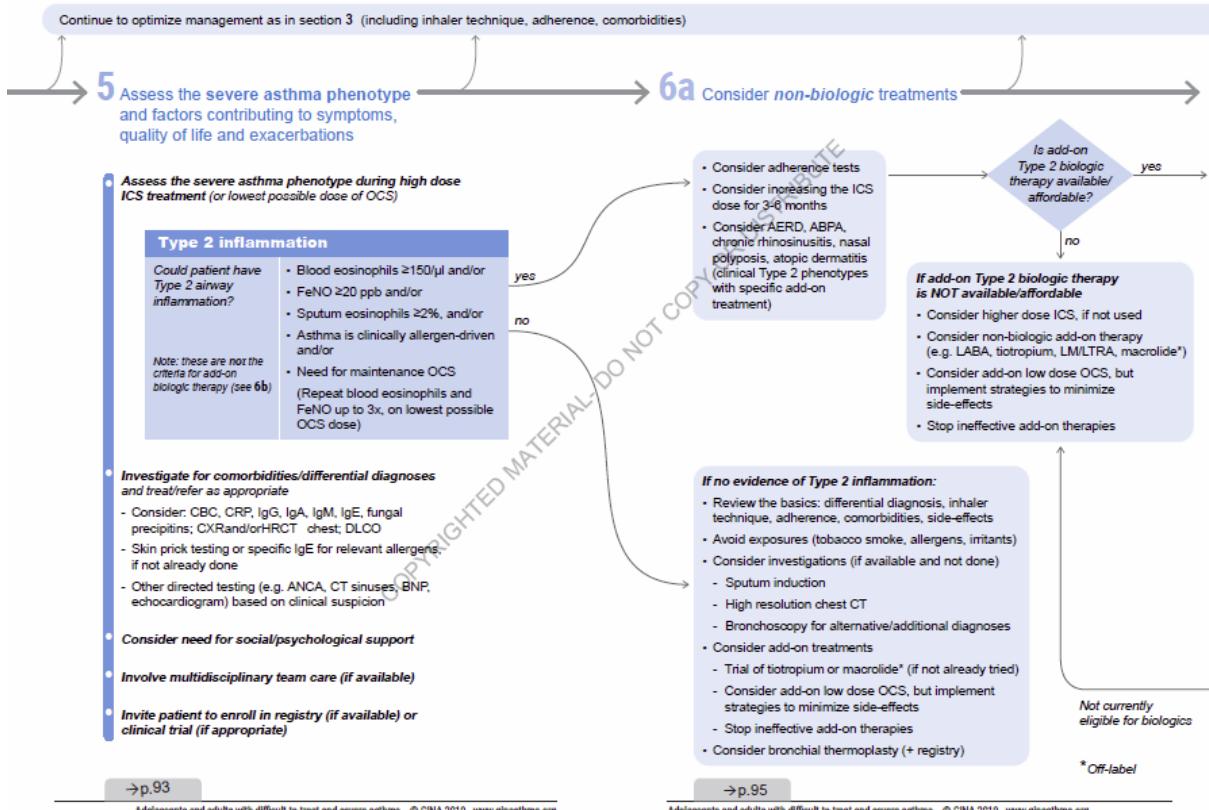
Box 3-16A

GP OR SPECIALIST CARE

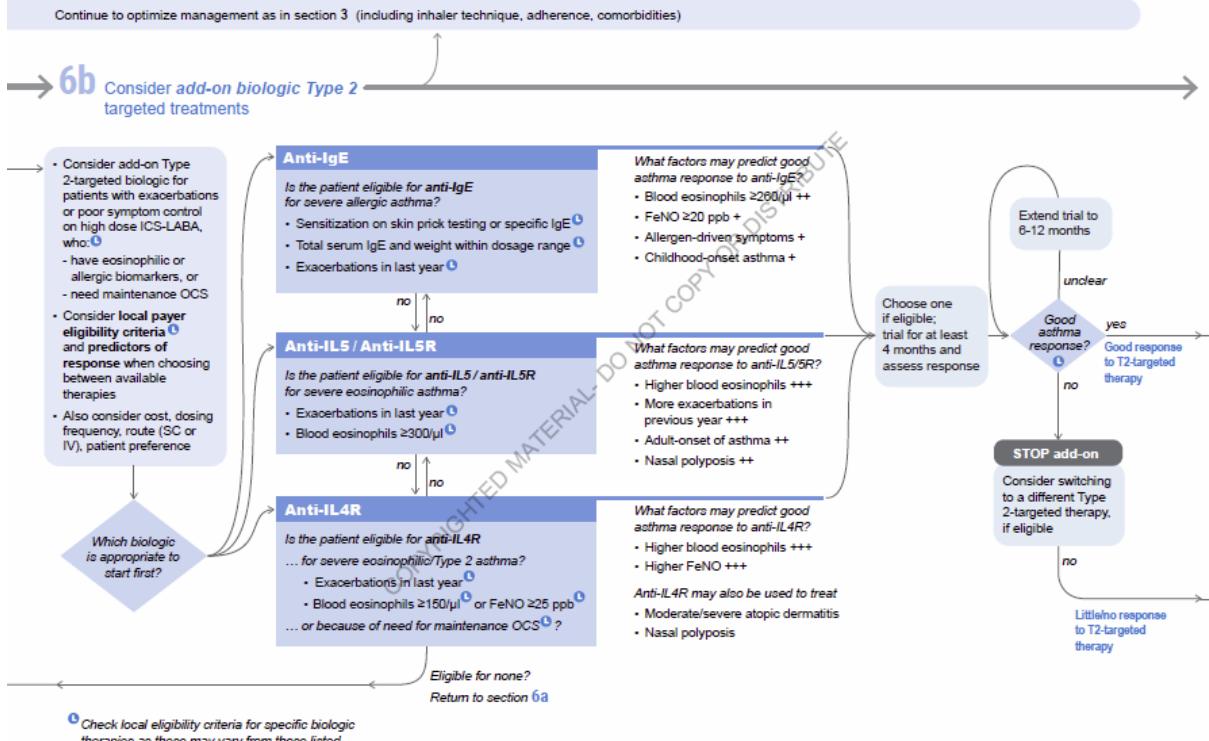
#### Investigate and manage adult and adolescent patients with difficult-to-treat asthma



## Assess and treat severe asthma phenotypes

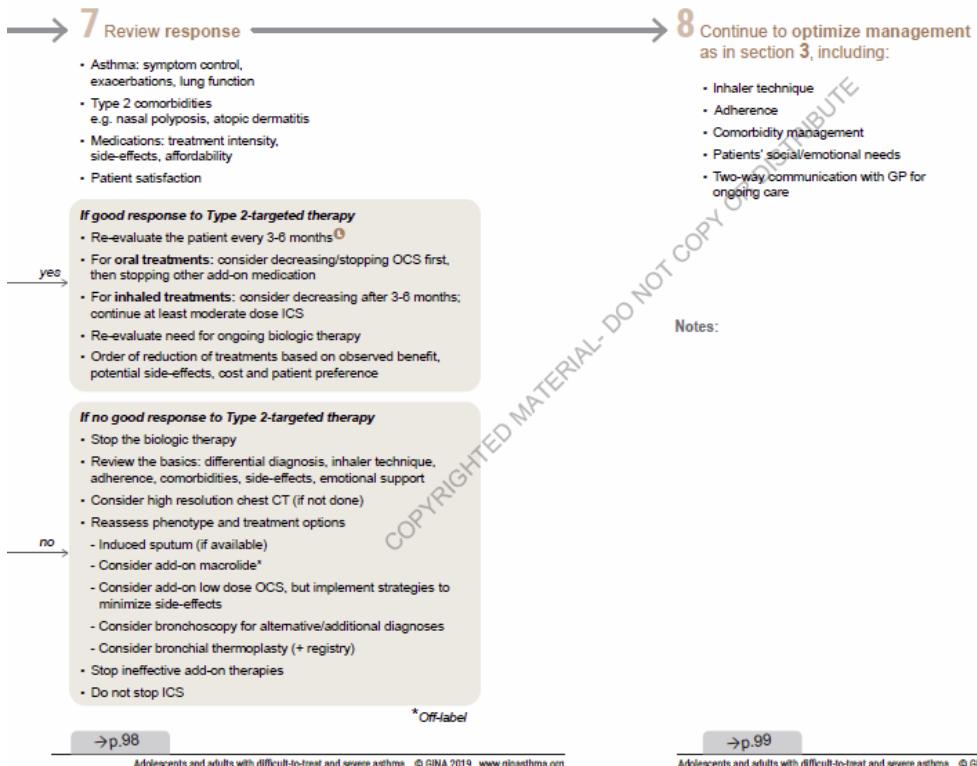


## Assess and treat severe asthma phenotypes cont'd



**Monitor / Manage severe asthma treatment**

Continue to optimize management



→ p.98

Adolescents and adults with difficult-to-treat and severe asthma © GINA 2019 www.ginasthma.org

→ p.99

Adolescents and adults with difficult-to-treat and severe asthma © GINA 2019 www.ginasthma.org

**SIGN, 2016 [21].**

*Scottish Intercollegiate Guidelines Network (SIGN) in Kooperation mit British Thoracic Society*  
British guideline on the management of asthma

**Leitlinienorganisation/Fragestellung**

The guideline considers asthma management in all patients with a diagnosis of asthma, although there is less evidence available for people at either age extreme.

**Methodik**Grundlage der Leitlinie

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.

Update: 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](http://www.brit-thoracic.org.uk)) and SIGN ([www.sign.ac.uk](http://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 <sup>++</sup>	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1 <sup>+</sup>	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1 <sup>-</sup>	Meta-analyses, systematic reviews, or RCTs with a high risk of bias High-quality systematic reviews of case-control or cohort studies
2 <sup>++</sup>	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 <sup>+</sup>	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 <sup>-</sup>	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	
<i>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.</i>	
A	At least one meta-analysis, systematic review, or RCT rated as 1 <sup>++</sup> , and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1 <sup>+</sup> , directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2 <sup>++</sup> , directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1 <sup>++</sup> or 1 <sup>+</sup>
C	A body of evidence including studies rated as 2 <sup>+</sup> , directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2 <sup>++</sup>
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2 <sup>-</sup>
GOOD PRACTICE POINTS	
<input checked="" type="checkbox"/>	Recommended best practice based on the clinical experience of the guideline development group

### **Emfehlungen**

#### **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)

## 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.<sup>435,464,465</sup>

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.<sup>453</sup>

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.<sup>466</sup>

>12  
years

1++

1++

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.<sup>467</sup>

>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.<sup>468</sup> 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.<sup>469,470</sup>

>12  
years

1++

1\*

1+

## OTHER APPROACHES

Theophyllines may improve lung function and symptoms, but side effects occur more commonly.<sup>444</sup>

>12  
years

1+

Slow-release β<sub>2</sub>agonist tablets may also improve lung function and symptoms, but side effects occur more commonly.<sup>443</sup>

1++

Addition of short-acting anticholinergics is generally of no value.<sup>445,472</sup> Addition of nedocromil is of marginal benefit.<sup>438,446</sup>

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<sub>2</sub> 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  $\beta_2$  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.<sup>467</sup> The following recommendations are largely based on extrapolation from trials of add-on therapy to ICS alone (see section 7.4).

D

D

If control remains inadequate on medium dose (adults) or low dose (children) of an inhaled corticosteroid plus a long-acting  $\beta_2$  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  $\beta_2$  agonist tablets, although caution needs to be used in patients already on long-acting  $\beta_2$  agonists, or
- add tiotropium (adults).

>12  
years  
1++

There are no controlled trials indicating which of these is the best option, although the potential for side effects is greater with theophyllines and  $\beta_2$  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.

Anmerkung zu Empfehlungen: Stufenschema siehe Anhang

## 4 Detaillierte Darstellung der Recherchestrategie

**Cochrane Library - Cochrane Database of Systematic Reviews (Issue 6 of 12) am 04.06.2019**

#	Suchfrage
1	[mh Asthma]
2	asthma*:ti
3	#1 OR #2
4	#3 with Cochrane Library publication date from Jun 2014 to Jun 2019, in Cochrane Reviews

**Systematic Reviews in Medline (PubMed) am 04.06.2019**

#	Suchfrage
1	,“asthma/therapy”[mh]
2	asthma*[ti]
3	(treatment*[tiab] OR treating[tiab] OR treated[tiab] OR treat[tiab] OR treats[tiab] OR treatab*[tiab] OR therapy[tiab] OR therapies[tiab] OR therapeutic*[tiab] OR monotherap*[tiab] OR polytherap*[tiab] OR pharmacotherap*[tiab] OR effect*[tiab] OR efficacy[tiab] OR management[tiab] OR drug*[tiab])
4	#1 OR (#2 AND #3)
5	(#4) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis [pt] OR meta-analysis [ti] OR systematic literature review [ti] OR this systematic review [tw] OR pooling project [tw] OR (systematic review [tiab] AND review [pt])) OR meta synthesis [ti] OR meta-analy*[ti] OR integrative review [tw] OR integrative research review [tw] OR rapid review [tw] OR umbrella review [tw] OR consensus development conference [pt] OR practice guideline [pt] OR drug class reviews [ti] OR cochrane database syst rev [ta] OR acp journal club [ta] OR health technol assess [ta] OR evid rep technol assess summ [ta] OR jbi database system rev implement rep [ta]) OR (clinical guideline [tw] AND management [tw]) OR ((evidence based[ti] OR evidence-based medicine [mh] OR best practice* [ti] OR evidence synthesis [tiab]) AND (review [pt] OR diseases category[mh] OR behavior and behavior mechanisms [mh] OR therapeutics [mh] OR evaluation studies[pt] OR validation studies[pt] OR guideline [pt] OR pmcbook)) OR ((systematic [tw] OR systematically [tw] OR critical [tiab] OR (study selection [tw]) OR (predetermined [tw] OR inclusion [tw] AND criteri* [tw])) OR exclusion criteri* [tw] OR main outcome measures [tw] OR standard of care [tw] OR standards of care [tw]) AND (survey [tiab] OR surveys [tiab] OR overview* [tw] OR review [tiab] OR reviews [tiab] OR search* [tw] OR handsearch [tw] OR analysis [ti] OR critique [tiab] OR appraisal [tw] OR (reduction [tw] AND (risk [mh] OR risk [tw]) AND (death OR recurrence))) AND (literature [tiab] OR articles [tiab] OR publications [tiab] OR publication [tiab] OR bibliography [tiab] OR bibliographies [tiab] OR published [tiab] OR pooled data [tw] OR unpublished [tw] OR citation [tw] OR citations [tw] OR database [tiab] OR internet [tiab] OR textbooks [tiab] OR references [tw] OR scales [tw] OR papers [tw] OR datasets [tw] OR trials [tiab] OR meta-analy* [tw] OR (clinical [tiab] AND studies [tiab]) OR treatment outcome [mh] OR treatment outcome [tw] OR pmcbook)) NOT (letter [pt] OR newspaper article [pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab]))) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR (((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND

	((evidence[tiab]) AND based[tiab]))))))
6	(#5) AND ("2014/06/01"[PDAT] : "3000"[PDAT])
7	(#6) NOT "The Cochrane database of systematic reviews"[Journal]
8	(#7) NOT retracted publication[ptyp]

### Leitlinien in Medline (PubMed) am 04.06.2019

#	Suchfrage
1	asthma[majr]
2	asthma*[ti]
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*[ti] OR recommendation*[ti])
5	(#4) AND ("2014/06/01"[PDAT] : "3000"[PDAT])
6	(#5) NOT retracted publication[ptyp]

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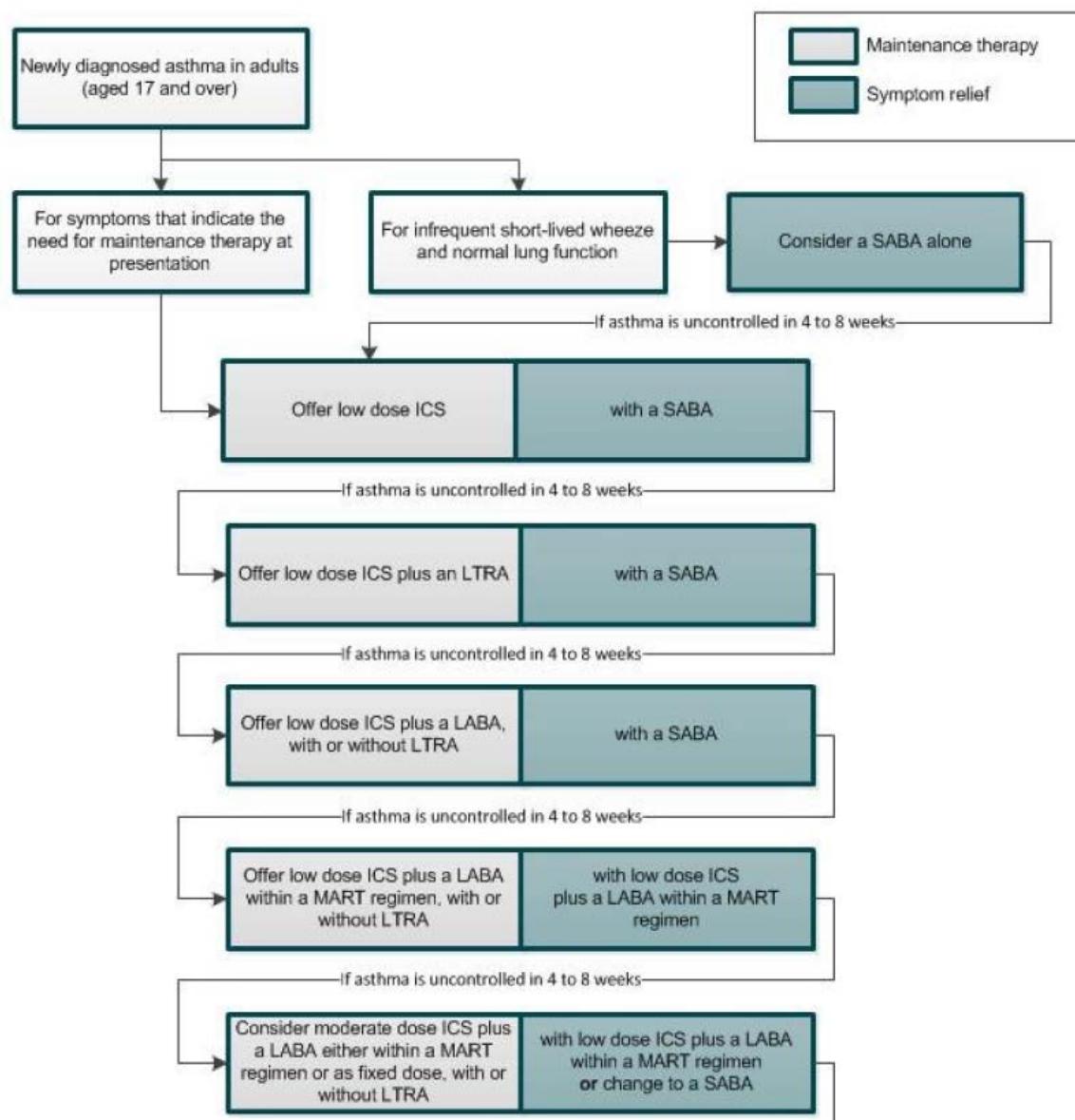
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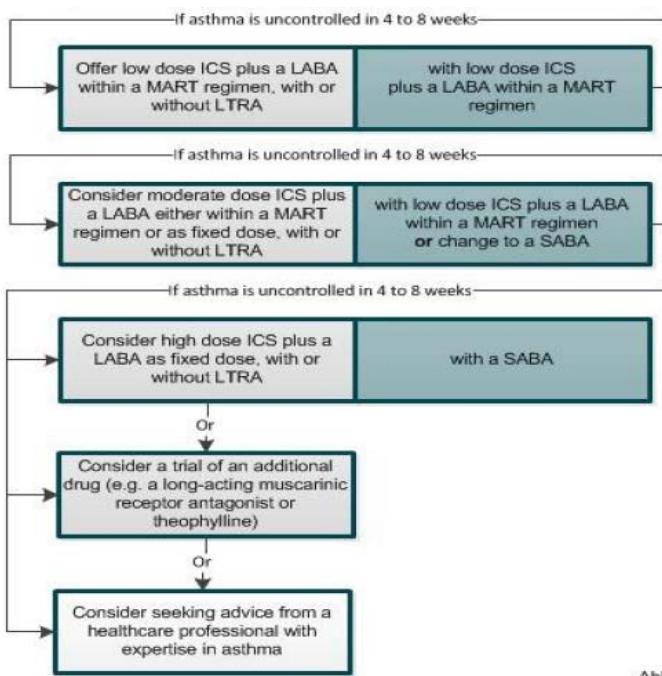
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## Anhang

### NICE, 2017 [18] Asthma: diagnosis, monitoring and chronic asthma management Algorithm C: Pharmacological treatment of chronic asthma in adults aged 17 and over





Abbreviations:  
 ICS, inhaled corticosteroid  
 LABA, long-acting beta agonist  
 LTRA, leukotriene receptor antagonist  
 MART, maintenance and reliever therapy  
 SABA, short-acting beta agonist

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