IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Reslizumab (asthma) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Reslizumab (Asthma) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 11 April 2017). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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[3] Table numbers start with "2" as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACQ	Asthma Control Questionnaire
ACT	appropriate comparator therapy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GINA	Global Initiative for Asthma
ICS	inhaled corticosteroids
IgE	immunoglobulin E
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LABA	long-acting beta-2 agonist
LTRA	leukotriene receptor antagonist
OCS	oral corticosteroid
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug reslizumab. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 16 January 2017.

Research question

The aim of the present report was to assess the added benefit of an add-on therapy with reslizumab in comparison with the appropriate comparator therapy (ACT) in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment.

The G-BA specified the following ACT:

- individually optimized treatment escalation of high-dose ICS and long-acting bronchodilators (long-acting beta-2 agonists, LABAs), if applicable with oral corticosteroids (OCS) (short-term) in their lowest effective dose or tiotropium or, if applicable in immunoglobulin E (IgE)-mediated pathogenesis of asthma, omalizumab in addition to high-dose ICS and long-acting bronchodilators (LABAs) and, if applicable, to OCS treatment

The approvals of the drugs and the Global Initiative for Asthma (GINA) graded scheme were to be taken into account. It was assumed that the therapeutic indication of reslizumab is represented in step 4 to step 5 (according to GINA).

The G-BA additionally specified that placebo or unchanged continuation of inadequate treatment of severe asthma, if the option for treatment escalation is still available, does not comply with the ACT in severe uncontrolled asthma.

The company did not completely concur with the ACT specified by the G-BA. It regarded the ACT options mentioned by the G-BA as equivalent alternatives and chose one of them. It specified individually optimized treatment escalation of high-dose ICS and LABAs, if applicable with OCS (short-term) in their lowest effective dose, as its comparator therapy, thus excluding treatment escalations with tiotropium or omalizumab from its comparator therapy.

This approach of the company was inadequate. The ACT specified by the G-BA was a treatment escalation tailored to the individual patient. The options mentioned by the G-BA

were no equivalent alternatives for the individual patients. Deviating from the company, the present assessment was therefore conducted in comparison with the G-BA's ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. A minimum study duration of 24 weeks was defined for the derivation of the added benefit.

Results

The company identified 2 randomized controlled trials (RCTs) for the assessment of the added benefit of reslizumab in adult patients with severe eosinophilic asthma: the studies C38072/3082 (3082) and C38072/3083 (3083). Both studies were conducted following a comparable protocol and are described together below. Both studies were unsuitable to derive conclusions on the added benefit of reslizumab in comparison with the ACT.

The studies 3082 and 3083 were multicentre, randomized, double-blind, placebo-controlled studies with a treatment duration of 52 weeks. The studies included patients between 12 and 75 years of age with confirmed diagnosis of asthma and blood eosinophil counts of at least 400 cells/µL before the start of the study whose symptoms were inadequately controlled with corticosteroids and who had had at least one exacerbation requiring OCS treatment in the previous year. The aim of the study was to compare efficacy and tolerability of reslizumab at a dosage of 3.0 mg/kg body weight versus placebo every 4 weeks. Study patients were to continue their ongoing asthma medication they had been taking at a stable dosage for at least 30 days before screening without modifications of dosage until the end of study.

For both studies, the company analysed a subpopulation of 284 patients in total, comprising 32% (3082) and 28% (3083) of the respective total study populations. The company excluded patients who did not concur with the inclusion criteria of the present research question because reslizumab is not approved for them. Overall, the definition of the relevant subpopulation of the company was adequate.

Appropriate comparator therapy not implemented in the studies presented

The studies 3082 and 3083 were unsuitable for the assessment of the added benefit of reslizumab in comparison with the ACT in the form of individually optimized treatment escalation with the different options specified by the G-BA. This was due to the fact that both studies did not implement the ACT because the specified treatment escalations were not conducted in the comparator arm, neither at the start of the studies nor during the studies. In the respective control arms, no treatment escalations were planned for the start of the study, whereas patients in the intervention arms received reslizumab as add-on therapy. According to the study description, no treatment escalation was mandated in the framework of the concomitant treatment either. Instead, the asthma medication used before screening was to be continued without dose adjustment and maintained at a stable dose in all study arms during the study.

The company stated in its dossier that initiation or escalation of OCS treatment was possible in case of deterioration of asthma symptoms and presented analyses on the OCS use during the study for both studies. According to these analyses, almost half of the patients in the placebo arms had received no adjustments to their OCS treatment (initiation or dose increase of an ongoing OCS treatment). In addition, many patients who initiated OCS treatment received this therapy for the acute treatment of an exacerbation. The comparator therapy was therefore not adequately implemented with respect to the escalation options with OCS. Escalations with tiotropium and omalizumab were not mandated in the studies.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

Table 2 presents a summary of the extent and probability of the added benefit of reslizumab.

Table 2: Reslizumab – extent and probability of added benefit

Therapeutic indication	Appropriate comparator therapy[a]	Extent and probability of added benefit
Add-on therapy in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus another medicinal product for maintenance treatment	Individually optimized treatment escalation of high-dose inhaled corticosteroids and long-acting bronchodilators (LABAs), if applicable with oral corticosteroids (short-term) in their lowest effective dose or tiotropium or, if applicable in immunoglobulin E-mediated pathogenesis of asthma, omalizumab in addition to high-dose inhaled corticosteroids and LABAs and, if applicable, to oral corticosteroid treatment	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; LABA: long-acting beta-2 agonist		

The G-BA decides on the added benefit.

[4] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, no added benefit, or less benefit). For further details see [1,2].

2.2 Research question

The aim of the present report was to assess the added benefit of an add-on therapy with reslizumab in comparison with the ACT in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose ICS plus another medicinal product for maintenance treatment.

The G-BA specified the following ACT:

- individually optimized treatment escalation of high-dose ICS and long-acting bronchodilators (LABAs), if applicable with OCS (short-term) in their lowest effective dose or tiotropium or, if applicable in IgE-mediated pathogenesis of asthma, omalizumab in addition to high-dose ICS and long-acting bronchodilators (LABAs) and, if applicable, to OCS treatment

The approvals of the drugs and the GINA graded scheme were to be taken into account. It was assumed that the therapeutic indication of reslizumab is represented in step 4 to step 5 (according to GINA) [3].

The G-BA additionally specified that placebo or unchanged continuation of inadequate treatment of severe asthma, if the option for treatment escalation is still available, does not comply with the ACT in severe uncontrolled asthma.

The company did not completely concur with the ACT specified by the G-BA. It regarded the ACT options mentioned by the G-BA as equivalent alternatives and chose one of them. It specified individually optimized treatment escalation of high-dose ICS and LABAs, if applicable with OCS (short-term) in their lowest effective dose, as its comparator therapy, thus excluding treatment escalations with tiotropium or omalizumab from its comparator therapy.

This approach of the company was inadequate. The ACT specified by the G-BA was a treatment escalation tailored to the individual patient. The options mentioned by the G-BA were no equivalent alternatives for the individual patients. Instead, it had to be checked for each individual patient which of the options mentioned by the G-BA constituted the individually optimized treatment escalation. Since a treatment deviating from the company's choice might be necessary due to individual criteria such as tolerability or pretreatments, limitation to one single option of treatment escalation is not meaningful. Deviating from the company, the present assessment was therefore conducted in comparison with the G-BA's ACT.

The company's approach did not affect the completeness of the study pool, however, because the company used the complete ACT in its inclusion criteria.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. A minimum study duration of 24 weeks was defined

for the derivation of the added benefit. This deviates from the company's approach, which used studies with a minimum duration of 52 weeks (see Section 2.7.2.1 of the full dossier assessment).

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on reslizumab (status: 4 November 2016)
- bibliographical literature search on reslizumab (last search on 1 November 2016)
- search in trial registries for studies on reslizumab (last search on 1 November 2016)

To check the completeness of the study pool:

- search in trial registries for studies on reslizumab (last search on 23 January 2017)

No relevant study was identified from the check.

The company identified 2 RCTs for the assessment of the added benefit of reslizumab in adult patients with severe eosinophilic asthma: the studies C38072/3082 (4-6) and C38072/3083 (6-8), hereinafter referred to as "3082" and 3083". Both studies were conducted following a comparable protocol and are described together below.

Studies 3082 and 3083

The studies 3082 and 3083 were multicentre, randomized, double-blind, placebo-controlled studies with a treatment duration of 52 weeks. The studies included patients between 12 and 75 years of age with confirmed diagnosis of asthma and blood eosinophil counts of at least 400 cells/µL before the start of the study whose symptoms were inadequately controlled with corticosteroids and who had had at least one exacerbation requiring OCS treatment in the previous year. Further inclusion criteria included a minimum Asthma Control Questionnaire (ACQ) score of 1.5 and a minimum ICS dose of 440 µg fluticasone or equivalent per day. In addition, the daily dose of OCS was limited to at most 10 mg.

The aim of the study was to compare efficacy and tolerability of reslizumab at a dosage of 3.0 mg/kg body weight versus placebo every 4 weeks. Study patients were to continue their ongoing asthma medication they had been taking at a stable dosage for at least 30 days before screening without modifications of dosage until the end of study. Further information on the studies 3082 and 3083 can be found in Table 8, Table 9 and Table 10 in Appendix A of the full dossier assessment.

Additional analyses for the benefit assessment

For both studies, the company analysed a subpopulation of 284 patients in total, comprising 32% (3082) and 28% (3083) of the respective total study populations. The company excluded patients who did not concur with the inclusion criteria of the present research question because reslizumab is not approved for them. This applied to patients under 18 years of age, patients who were not receiving a high dosage of ICS treatment at study entry and patients who were receiving no LABAs as additional control medication. The company defined high-dose ICS according to the information provided in the GINA guideline [9] and under consideration of the SPCs [10-15]. Overall, the definition of the relevant subpopulation of the company was adequate.

Appropriate comparator therapy not implemented in the studies presented

The studies 3082 and 3083 were unsuitable for the assessment of the added benefit of reslizumab in comparison with the ACT in the form of individually optimized treatment escalation with the different options specified by the G-BA. This was due to the fact that both studies did not implement the ACT because the specified treatment escalations were not conducted in the comparator arm, neither at the start of the studies nor during the studies. In the respective control arms, no treatment escalations were planned for the start of the study, whereas patients in the intervention arms received reslizumab as add-on therapy. According to the study description, no treatment escalation was mandated in the framework of the concomitant treatment either. Instead, the asthma medication used before screening was to be continued without dose adjustment and maintained at a stable dose in all study arms during the study. Hence the ACT of individually optimized treatment escalation was not implemented.

This deviates from the assessment of the company, which regarded the ACT as implemented in both studies presented:

- The company argued that, due to the long history of asthma of the patients included, treatment escalation options had been exhausted before the study and that it could be assumed that the study patients already had individually optimized, albeit not complete, symptom control at the start of the study. Since the patients included were required to have received stable asthma medication for 30 days at the start of the study, the company regarded treatment escalation not to be indicated at the start of the study.
- In addition, OCS were allowed both as continuation of the maintenance treatment and for the treatment of deterioration of symptoms.

This rationale was not followed. The G-BA specified for the ACT that placebo or unchanged continuation of inadequate treatment of severe asthma, if the option for treatment escalation is still available, does not comply with the ACT. Instead, the company named several treatment options for individually optimized treatment escalation in its specification of the ACT. The company provided no reasons why these treatment options were not possible for the patients

included. At the same time, there was inadequate asthma control in the study populations, indicated by a mean ACQ symptom score of almost 3 and a mean number of asthma exacerbations in the previous year of more than 2 (see Table 10 in Appendix A of the full dossier assessment) [3,16]. The company itself described that such patients had an increased risk of exacerbations [17]. The treatment used before the start of the study was therefore inadequate to ensure the treatment goal, which was asthma control. In this situation, guidelines recommend treatment escalation to achieve symptom control and prevent exacerbations [3,16].

Against the background of missing treatment escalation in the control arm at the start of the study, it is shown below for the different treatment options whether, at least in the further course of the study, the comparator arms offered options of treatment escalation that could be used as an implementation of the ACT.

Options of treatment escalation in the studies 3082 and 3083

Treatment escalation using tiotropium or omalizumab

Tiotropium was an option for treatment escalation within the G-BA's ACT. The company noted that tiotropium had no approval for the therapeutic indication of asthma when the study was conducted. A total of 26 patients (9%) in the approval-compliant subpopulations of both studies were actually already receiving tiotropium as off-label treatment at study entry. Tiotropium was not an option for treatment escalation in the framework of the studies 3082 and 3083, however.

Omalizumab can be used in patients with IgE-mediated pathogenesis of asthma for treatment escalation and was also a treatment option of the G-BA's ACT. In the studies presented, omalizumab was not allowed in the 6 months before the start of the study and during the studies. Hence this treatment option was also not available to the patients in the framework of the studies. The company also provided no information on the number of included patients for whom omalizumab would have been a possible treatment escalation.

Hence both ACT options described above were not implemented in the studies 3082 and 3083.

Treatment escalation with oral corticosteroids

Another option of treatment escalation according to the G-BA's ACT was short-term treatment escalation with OCS at their lowest effective dose. Low-dose OCS can be indicated as additional control medication (maintenance treatment) for several weeks to months for patients at high risk of exacerbation as the ones described in the therapeutic indication of reslizumab and included in the studies [3].

In the studies 3082 and 3083, OCS maintenance treatment was allowed as concomitant medication if it had been stable for 30 days before screening and could be continued without adjustments during the course of the study (see Table 9 of the full dossier assessment). The

study documents contained no further information about whether initiation or escalation of OCS maintenance treatment was possible in the framework of the studies.

In its dossier, the company stated that initiation or escalation of OCS treatment had been possible for deterioration of asthma symptoms. It additionally presented analyses on the use of OCS during the study (see Table 3). It provided no information on whether initiation or dose increase of OCS treatment was targeted at improved symptom control or prevention of exacerbations or whether it was used to treat an acute exacerbation.

Table 3: OCS use in the studies included by the company – RCT, direct comparison: reslizumab vs. placebo

Study	3082		3083	
Use Category	Reslizumab	Placebo	Reslizumab	Placebo
	N = 80	N = 76	N = 59	N = 69
OCS use at the start of the study[a]				
n (%)	13 (16)	26 (34)	10 (17)	8 (12)
Initiation of OCS treatment during the study				
n (%)	33 (41.3)	29 (38.2)	18 (30.5)	28 (40.6)
Duration of OCS treatment (days)				
Mean (SD)	25.9 (66.7)	26.7 (28.0)	11.1 (7.3)	56.1 (120.3)
Median [min; max]	10.0 [3.0; 392.0]	12.0 [2.0; 117.0]	10.0 [1.0; 30.0]	12.0 [3.0; 431.0]
Betamethasone dose [mg/day]				
Mean (SD)	1.5 (ND)	–[b]	–[b]	–[b]
Median [min; max]	1.5 [1.5; 1.5]	–[b]	–[b]	–[b]
Methylprednisolone dose [mg/day]				
Mean (SD)	16.0 (6.8)	27.1 (5.9)	18.7 (4.6)	19.9 (7.9)
Median [min; max]	16.0 [11.2; 20.8]	29.2 [18.4; 32.0]	16.0 [16.0; 24.0]	22.2 [8.5; 32.0]
Prednisone and prednisolone dose (mg/day)				
Mean (SD)	30.8 (10.3)	32.6 (8.1)	28.5 (18.5)	27.5 (9.7)
Median [min; max]	30.0 [6.3; 50.0]	34.9 [12.2; 45.0]	23.3 [5.0; 70.0]	30.0 [5.0; 50.0]
Dose increase of ongoing OCS treatment during the study				
n (%)	5 (6.3)	14 (18.4)	2 (3.4)	5 (7.2)
Duration of OCS treatment (days)				
Mean (SD)	124.8 (117.7)	227.3 (121.6)	252.5 (16.3)	170.0 (154.4)
Median [min; max]	84.0 [10.0; 297.0]	282.0 [7.0; 377.0]	252.5 [241.0; 264.0]	193.0 [8.0; 327.0]
Deflazacort dose [mg/day]				
Mean (SD)	–[b]	48.8 (ND)	–[b]	–[b]
Median [min; max]	–[b]	48.8 [48.8; 48.8]	–[b]	–[b]
Methylprednisolone dose [mg/day]				
Mean (SD)	4.2 (ND)	10.2 (3.9)	–[b]	14.1 (14.0)
Median [min; max]	4.2 [4.2; 4.2]	9.5 [5.9; 16.0]	–[b]	14.1 [4.2; 24.0]
Prednisone and prednisolone dose (mg/day)				
Mean (SD)	22.4 (9.7)	15.3 (10.1)	8.8 (4.4)	10.5 (0.5)
Median [min; max]	22.7 [12.7; 31.4]	12.1 [6.9; 37.5]	8.8 [5.7; 12.0]	10.6 [10.0; 11.0]

a: Information based on the eCRF. There are also data based on the information recorded at randomization using IRT. The deviation between the information is not serious and not relevant for the present assessment, however.

b: The drug was not administered in the study arm.

eCRF: electronic case report form; IRT: interactive response technology; max: maximum; min: minimum; N: number of patients in the subpopulation analysed by the company; n: number of patients in the category; ND: no data; OCS: oral corticosteroid; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

During the study, new OCS treatment was initiated in a total of 57 patients (39%) in the placebo arms of the subpopulations of both studies. Due to the short median treatment duration of 12 days it can be assumed, however, that this was treatment of an acute exacerbation in at least half of the patients. Another 19 patients (13%) received dose increase of their ongoing OCS treatment. Hence almost half (48%) of the patients in the placebo arms had no adjustment to their OCS treatment – neither at the start of the study nor during the study – although, according to the inclusion criteria and patient characteristics, they had poor symptom control already at study entry. In addition, many patients who initiated OCS treatment received this therapy for the acute treatment of an exacerbation.

The comparator therapy was therefore not adequately implemented also with respect to the escalation options with OCS.

It should be additionally noted that the occurrence of clinical asthma exacerbation constituted the primary outcome of the studies. Results for this outcome are not meaningfully interpretable, however, if the patients in one study arm (intervention arm) receive treatment escalation to prevent exacerbations, whereas patients in the other study arm (control arm) receive treatment escalation in many cases only when exacerbation and thus the outcome of the study occurs.

Further limitations of the studies 3082 and 3083

The studies presented had the following further limitations, which have no consequences for the assessment because the studies were not relevant for the assessment for the reasons stated above.

In the subpopulation analysed by the company, a total of 34% of the patients were treated with leukotriene antagonists (leukotriene receptor antagonists [LTRAs], particularly montelukast) or chromones (cromoglicic acid) at study entry. In Germany, montelukast and cromoglicic acid are not approved for severe asthma so that the use of these drugs in the study patients was not in compliance with the approval [18,19].

The inclusion of these patients in the benefit assessment was inadequate. The company itself stated that patients without LTRA or chromone treatment in Germany represented the patient group treated in compliance with the approval and conducted subgroup analyses planned post hoc to investigate the effect modification by the characteristic “use of LTRAs or chromones at the start of the study”.

Another problem was that, concurring with the inclusion criteria, patients with OCS maintenance treatment were included in the studies only if the dosage of the ongoing OCS treatment was ≤ 10 mg prednisone or equivalent per day. The studies therefore allowed no conclusions for particularly severely ill patients who might require treatment with higher doses of OCS.

2.4 Results on added benefit

The company presented no relevant data for the assessment of the added benefit of reslizumab in its dossier. This resulted in no hint of an added benefit of reslizumab in comparison with the ACT; an added benefit is therefore not proven.

2.5 Extent and probability of added benefit

The result of the assessment of the added benefit of reslizumab in comparison with the ACT is shown in Table 4.

Table 4: Reslizumab – extent and probability of added benefit

Therapeutic indication	**Appropriate comparator therapy**[a]	**Extent and probability of added benefit**
Add-on therapy in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus another medicinal product for maintenance treatment	Individually optimized treatment escalation of high-dose inhaled corticosteroids and long-acting bronchodilators (LABAs), if applicable with oral corticosteroids (short-term) in their lowest effective dose or tiotropium or, if applicable in immunoglobulin E-mediated pathogenesis of asthma, omalizumab in addition to high-dose inhaled corticosteroids and LABAs and, if applicable, to oral corticosteroid treatment	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; LABA: long-acting beta-2 agonist		

This assessment deviates from that of the company, which derived proof of a minor added benefit of reslizumab on the basis of the evidence presented.

The G-BA decides on the added benefit.

2.6 List of included studies

Not applicable as the company presented no relevant data for the benefit assessment.

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Please see full dossier assessment for full reference list.

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