IQWiG Reports – Commission No. 19-74

Dupilumab (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 *Dupilumab (Asthma) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 November 2019). 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.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Dupilumab (asthma) – Benefit assessment according to §35a Social Code Book V

Commissioning agency:
Federal Joint Committee

Commission awarded on:
29 August 2019

Internal Commission No.:
A19-74

Address of publisher:
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice:

- Thomas O. F. Wagner, Frankfurter Referenzzentrum für Seltene Erkrankungen (FRZSE [Frankfurt Expert Center for Rare Diseases]), University Hospital Frankfurt, Germany

IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

IQWiG employees involved in the dossier assessment:

- Anne Hüning
- Katharina Hirsch
- Ana Liberman
- Sabine Ostlender
- Min Ripoll
- Dorothea Sow
- Corinna ten Thoren
- Beate Wieseler

Keywords: dupilumab, asthma, benefit assessment

Table of contents

List of tables[2]

Page

[2] 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
CPGs	clinical practice guidelines
FeNO	fractionated exhaled nitric oxide
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
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
LAMA	long-acting muscarinic antagonist
OCS	oral corticosteroids
ppb	parts per billion
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

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 dupilumab. The assessment was based on a dossier compiled by the company. The dossier was sent to IQWiG on 29 August 2019.

Research question

The aim of the present report is the assessment of the added benefit of an add-on maintenance treatment with dupilumab in comparison with the appropriate comparator therapy (ACT) in adolescents aged 12 to 17 years and adults with inadequately controlled severe type 2 inflammation asthma, characterized by an increased number of eosinophilic granulocytes and/or increased fractionated exhaled nitric oxide [FeNO] values, who already receive high-dose inhaled corticosteroids (ICS) and at least one further drug as maintenance treatment.

Two research questions resulted for the benefit assessment in accordance with the G-BA's specification of the ACT. These are presented in Table 2.

Table 2: Research question of the benefit assessment of dupilumab

Research question	Subindication	ACT[a]
1	Adolescents aged 12 to 17 years with inadequately controlled severe type 2 inflammation asthma[b], who already receive high-dose ICS and at least one further drug as maintenance treatment[c]	Individual treatment escalation[d] under consideration of the prior therapy choosing from: ▪ high-dose ICS and LABA and LAMA or ▪ high-dose ICS and LABA and possibly LAMA and omalizumab[e]
2	Adults with inadequately controlled severe type 2 inflammation asthma[b], who already receive high-dose ICS and at least one further drug as maintenance treatment[c]	Individual treatment escalation[d] under consideration of the prior therapy and the pathogenesis of asthma choosing from: ▪ high-dose ICS and LABA and LAMA or ▪ high-dose ICS and LABA and possibly LAMA and omalizumab[e] or ▪ high-dose ICS and LABA and possibly LAMA and mepolizumab[e] or reslizumab[e] or benralizumab[e]

a: Presentation of the ACT specified by the G-BA.
b: Characterized by an increased number of eosinophilic granulocytes and/or increased FeNO values.
c: Treatment with dupilumab was only indicated in addition to high-dose ICS and at least one further drug for maintenance treatment.
d: According to the G-BA, the step-by-step scheme for drug treatment of the NVL on asthma 2018 [3] was to be considered. It is assumed that in the therapeutic indication of dupilumab the patients of research question 1 are represented in steps 5 to 6 of the step-by-step scheme for drug treatment for children and adolescents, and the patients of research question 2 are represented in steps 4 to 5 of the step-by-step scheme for drug treatment for adults. The therapeutic indication also comprised patients for whom there was no further escalation option for their ongoing treatment.
e: As far as the criteria required for the application are met.
ACT: appropriate comparator therapy; FeNO: fractionated exhaled nitric oxide; G-BA: Federal Joint Committee; ICS: inhaled corticosteroid; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist; NVL: Nationale VersorgungsLeitlinie (National Care Guideline)

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used for the derivation of the added benefit.

Results

With its information retrieval, the company identified the RCTs DRI12544, QUEST and VENTURE and used these studies for the joint assessment of the added benefit of dupilumab in adolescents and adults.

Research question 1: Adolescents aged 12 to 17 with inadequately controlled severe type 2 inflammation asthma

The company did not investigate research question 1 separately, but jointly considered adolescent and adult patients in the studies DRI12544, QUEST and VENTURE presented by it.

The populations of the presented studies considered by the company comprised no or only few adolescents (DRI12544: no adolescents; QUEST: 2.5%; VENTURE: approx. 1%). The data

available on common populations of adolescents and adults are thus unsuitable for the assessment of the added benefit of dupilumab in research question 1. Moreover, the data available for the assessment of the added benefit of dupilumab in research question 1 are not relevant, because the ACT specified for adolescents was not implemented in the studies presented by the company.

In its dossier, the company altogether presented no relevant data for the assessment of the added benefit of dupilumab as add-on maintenance treatment in adolescents aged 12 to 17 years with inadequately controlled severe type 2 inflammation asthma, who already receive high-dose ICS and at least one further drug as maintenance treatment, in comparison with the ACT. This resulted in no hint of an added benefit of dupilumab in comparison with the ACT; an added benefit is therefore not proven.

Research question 2: Adults with inadequately controlled severe type 2 inflammation asthma

The company used the RCTs DRI12544, QUEST and VENTURE also for research question 2 and considered the patient groups of adolescents and adults together.

Study characteristics

The study DRI12544 is a randomized, double-blind phase IIb study on the comparison of four different dosages of dupilumab with placebo. The study included adult patients with uncontrolled moderate to severe asthma who already received treatment with medium-dose or high-dose ICS and long-acting beta-2 agonist (LABA) at a stable dosage. Inclusion of patients receiving oral corticosteroid (OCS) maintenance treatment was not allowed. Moreover, the patients had experienced worsening of their asthma disease within the last year prior to the start of the study, defined as ≥ 1 treatment with systemic steroids or hospitalization or emergency treatment due to the worsening of their symptoms.

The QUEST study is a randomized, double-blind, phase 3 study on the comparison of two different dupilumab dosages with placebo. Patients 12 years of age and older with uncontrolled moderate to severe asthma who already received ongoing treatment with medium-dose or high-dose ICS and one or two further control medications (e.g. LABA) at a stable dosage were randomly allocated to the study. Moreover, the included patients had experienced worsening of their asthma within the last year before the start of the study, which was defined by ≥ 1 treatment with systemic steroids or hospitalization or emergency treatment due to a deterioration of their symptoms.

The VENTURE study is a randomized, double-blind phase 3 study on the comparison of dupilumab versus placebo in patients 12 years of age and older with uncontrolled severe asthma, who received ongoing asthma treatment with high-dose ICS and one or two further control medications at a stable dosage and who received regular treatment with OCS.

ACT not implemented in the presented studies DRI12544, QUEST and VENTURE

The ACT was not implemented in the studies DRI12544, QUEST and VENTURE, because treatment escalations in the comparator arms were neither performed at the start nor during the studies.

Patients included in studies DRI12544, QUEST and VENTURE had inadequately controlled asthma despite their ongoing asthma treatment. In this situation, the guidelines recommend treatment escalation. In the respective control arms, no treatment escalation was planned at the start of the study, whereas patients in the intervention arms received dupilumab as add-on therapy. According to the study planning, no treatment escalation was mandated in the framework of the concomitant treatment either. Instead, the ongoing asthma treatment administered at a stable dosage prior to the screening was to be continued in all study arms. Thereby, it can be inferred from the study documents that the presented studies included patients who were to undergo treatment escalation due to their uncontrolled severe asthma. Depending on the characteristics of their asthma disease (e.g. number of eosinophils in the blood) and on their prior therapy, a relevant number of patients were candidates for treatment escalation with the options of the ACT (long-acting muscarinic antagonist [LAMA], omalizumab, anti-IL-5 [receptor]antibodies). There is no suitable information available on the extent to which the studies included patients for whom escalation of their ongoing asthma therapy was impossible and for whom the comparator therapy used in the studies thus represented the ACT. Hence, the ACT was not implemented in any of the studies presented. The effects observed in the studies DRI12544, QUEST and VENTURE thus permit no conclusion on the added benefit of dupilumab.

In its dossier, the company altogether presented no relevant data for the assessment of the added benefit of dupilumab as add-on maintenance treatment in adults with inadequately controlled severe type 2 inflammation asthma, who already receive high-dose ICS and at least one further drug as maintenance treatment, in comparison with the ACT. This resulted in no hint of an added benefit of dupilumab in comparison with the ACT; an added benefit is therefore not proven for this research question.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 shows a summary of probability and extent of the added benefit of dupilumab.

[3] 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, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Dupilumab – probability and extent of added benefit

Research question	Subindication	ACT[a]	Probability and extent of added benefit
1	Adolescents aged 12 to 17 years with inadequately controlled severe type 2 inflammation asthma[b], who already receive high-dose ICS and at least one further drug as maintenance treatment[c]	Individual treatment escalation[d] under consideration of the prior therapy choosing from: ▪ high-dose ICS and LABA and LAMA or ▪ high-dose ICS and LABA and possibly LAMA and omalizumab[e]	Added benefit not proven
2	Adults with inadequately controlled severe type 2 inflammation asthma[b], who already receive high-dose ICS and at least one further drug as maintenance treatment[c]	Individual treatment escalation[d] under consideration of the prior therapy and the pathogenesis of asthma choosing from: ▪ high-dose ICS and LABA and LAMA or ▪ high-dose ICS and LABA and possibly LAMA and omalizumab[e] or ▪ high-dose ICS and LABA and possibly LAMA and mepolizumab[e] or reslizumab[e] or benralizumab[e]	Added benefit not proven

a: Presentation of the ACT specified by the G-BA.
b: Characterised by an increased number of eosinophilic granulocytes and/or increased FeNO values.
c: Treatment with dupilumab was only indicated in addition to high-dose ICS and at least one further drug for maintenance treatment.
d: According to the G-BA, the step-by-step scheme for drug treatment of the NVL on asthma 2018 [3] was to be considered. It is assumed that in the therapeutic indication of dupilumab the patients of research question 1 are represented in steps 5 to 6 of the step-by-step scheme for drug treatment for children and adolescents, and the patients of research question 2 are represented in steps 4 to 5 of the step-by-step scheme for drug treatment for adults. The therapeutic indication also comprises patients for whom there is no further escalation option of their ongoing treatment.
e: As far as the criteria required for the application are met.
ACT: appropriate comparator therapy; FeNO: fractionated exhaled nitric oxide; G-BA: Federal Joint Committee; ICS: inhaled corticosteroid; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist; NVL: Nationale VersorgungsLeitlinie (National Care Guideline)

The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report is the assessment of the added benefit of an add-on maintenance treatment with dupilumab in comparison with the ACT in adolescents aged 12 to 17 years and adults with inadequately controlled severe type 2 inflammation asthma, characterized by an increased number of eosinophilic granulocytes and/or increased FeNO values, who already receive high-dose ICS and at least one further drug as maintenance treatment.

Two research questions resulted for the benefit assessment in accordance with the G-BA's specification of the ACT. These are presented in Table 4.

Table 4: Research questions of the benefit assessment of dupilumab

Research question	Subindication	ACT[a]
1	Adolescents aged 12 to 17 years with inadequately controlled severe type 2 inflammation asthma[b], who already receive high-dose ICS and at least one further drug as maintenance treatment[c]	Individual treatment escalation[d] under consideration of the prior therapy choosing from: ▪ high-dose ICS and LABA and LAMA or ▪ high-dose ICS and LABA and possibly LAMA and omalizumab[e]
2	Adults with inadequately controlled severe type 2 inflammation asthma[b], who already receive high-dose ICS and at least one further drug as maintenance treatment[c]	Individual treatment escalation[d] under consideration of the prior therapy and the pathogenesis of asthma choosing from: ▪ high-dose ICS and LABA and LAMA or ▪ high-dose ICS and LABA and possibly LAMA and omalizumab[e] or ▪ high-dose ICS and LABA and possibly LAMA and mepolizumab[e] or reslizumab[e] or benralizumab[e]

a: Presentation of the ACT specified by the G-BA.
b: Characterised by an increased number of eosinophilic granulocytes and/or increased FeNO values.
c: Treatment with dupilumab was only indicated in addition to high-dose ICS and at least one further drug for maintenance treatment.
d: According to the G-BA, the step-by-step scheme for drug treatment of the NVL on asthma 2018 [3] was to be considered. It is assumed that in the therapeutic indication of dupilumab the patients of research question 1 are represented in steps 5 to 6 of the step-by-step scheme for drug treatment for children and adolescents, and the patients of research question 2 are represented in steps 4 to 5 of the step-by-step scheme for drug treatment for adults. The therapeutic indication also comprised patients for whom there was no further escalation option for their ongoing treatment.
e: As far as the criteria required for the application are met.
ACT: appropriate comparator therapy; FeNO: fractionated exhaled nitric oxide; G-BA: Federal Joint Committee; ICS: inhaled corticosteroid; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist; NVL: Nationale VersorgungsLeitlinie (National Care Guideline)

The company followed the specification of the ACT for both research questions. However, deviating from the G-BA, the company considered adolescents and adults together as one patient population (see Section 2.7.2 of the full dossier assessment). Concurring with the G-BA's specification, the present assessment was conducted for research question 1 (adolescents aged 12 to 17 years) and research question 2 (adults).

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks were used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

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 dupilumab (status: 5 July 2019)
- bibliographical literature search on dupilumab (last search on 4 July 2019)
- search in trial registries for studies on dupilumab (last search on 25 July 2019)

To check the completeness of the study pool:

- search in trial registries for studies on dupilumab (last search on 10 September 2019)

The check of the completeness of the study pool produced no relevant studies on the comparison of dupilumab versus the ACT for any of the research questions. In contrast to this, the company identified the RCTs DRI12544 [4-8], QUEST [9-13] and VENTURE [14-18] and used these studies for the joint assessment of the added benefit of dupilumab in adolescents and adults.

Moreover, the company described potential indirect comparisons for the assessment of the added benefit of dupilumab in comparison with mepolizumab, reslizumab and benralizumab, but did not perform these comparisons due to the lack of similarity of the studies (see Section 2.7.3.2 of the full dossier assessment).

The data presented from the RCTs DRI12544, QUEST and VENTURE as well as the indirect comparisons aspired by the company are not suitable for the assessment of the added benefit of dupilumab versus the ACT in research questions 1 and 2. This is explained for the individual research questions (see Sections 2.4 and 2.5).

2.4 Research question 1: Adolescents aged 12 to 17 with inadequately controlled severe type 2 inflammation asthma

In the presented studies DRI12544, QUEST and VENTURE (for the description of the studies, see Section 2.5), the company did not investigate research question 1 separately, but jointly considered adolescent and adult patients. In doing so, it only considered those intervention arms in which dupilumab was used in accordance with the approval. Moreover, the company only considered patients who were being treated with a high ICS dose in addition to a further control medication (see Section 2.5) upon study inclusion. These populations of the studies presented considered by the company comprised no or few adolescents:

- In accordance with the inclusion criteria, study DRI12544 included no adolescents.
- In the QUEST study, a total of 12 adolescents (2.5%) were included in the subpopulation used by the company, i.e. at the same proportion in the dupilumab arm and the comparator arm.
- The VENTURE study, in which all patients received high ICS doses, included a total of 3 adolescents (approx. 1%), 1 adolescent in the intervention arm and 2 adolescents in the comparator arm.

In the dossier, separate analyses for adolescents aged 12 to 17 years are only available as subgroup analyses from the QUEST study. The company did not use these analyses for the investigation of an added benefit in this research question.

The joint patient population of adolescents and adults used by the company is unsuitable for the derivation of an added benefit for the patient group of adolescents (see Section 2.7.2 of the full dossier assessment). Moreover, the data available for the assessment of the added benefit of dupilumab in research question 1 are irrelevant, because the following ACT specified for adolescents was not implemented in the studies presented by the company:

Individual treatment escalation choosing from

- high-dose ICS and LABA and LAMA
- high-dose ICS and LABA and possibly LAMA and omalizumab.

See Section 2.5 for a detailed discussion of the implementation of the above options of the ACT in the DRI12544, QUEST and VENTURE studies .

In summary, no suitable data were available for the assessment of research question 1.

2.4.1 Results on added benefit

In its dossier, the company altogether presented no relevant data for the assessment of the added benefit of dupilumab as add-on maintenance treatment in adolescents aged 12 to 17 years with inadequately controlled severe type 2 inflammation asthma, who already receive high-dose ICS and at least one further drug as maintenance treatment, in comparison with the ACT. This resulted in no hint of an added benefit of dupilumab in comparison with the ACT; an added benefit is therefore not proven.

2.4.2 Probability and extent of added benefit

Since data suitable for the assessment of the added benefit of dupilumab versus the ACT are not available for adolescents aged 12 to 17 years with inadequately controlled severe type 2 inflammation asthma, who already receive high-dose ICS and at least one further drug as maintenance treatment, an added benefit of dupilumab is not proven for this research question.

This deviates from the assessment of the company, which derived proof of major added benefit for the joint patient population of adolescents and adults on the basis of the subpopulations of patients with high ICS doses from the studies DRI12544 and QUEST used by it as well as of the total population of the VENTURE study. The company provided no separate information on the added benefit for the patient population of the adolescents aged 12 to 17 years relevant for research question 1.

2.4.3 List of included studies

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

2.5 Research question 2: Adults with inadequately controlled severe type 2 inflammation asthma

The company used the RCTs DRI12544, QUEST and VENTURE for the assessment of an added benefit for its jointly considered patient group of adolescents and adults. The data on the studies presented by the company were irrelevant for assessing the added benefit of dupilumab for research question 2. Hereinafter, the studies included by the company are described in more detail, providing reasons why the data presented from these studies were unsuitable for the assessment of the added benefit of dupilumab in comparison with the ACT.

Study characteristics

Study DRI12544

The study DRI12544 is a randomized, double-blind phase IIb study on the comparison of four different dosages of dupilumab with placebo. The study included adult patients with uncontrolled moderate to severe asthma who already received treatment with medium-dose or high-dose ICS and stable LABA dosages. Inclusion of patients receiving OCS maintenance treatment was not allowed. Moreover, the patients had experienced worsening of their asthma disease within the last year prior to the start of the study, defined as ≥ 1 treatment with systemic steroids or hospitalization or emergency treatment due to the worsening of their symptoms.

A total of 776 patients of the study were randomly assigned (1:1:1:1:1) to treatment with dupilumab 300 mg every two weeks (N = 157), dupilumab 200 mg every two weeks (N = 150), dupilumab 300 mg every four weeks (N = 157), dupilumab 200 mg every four weeks (N = 154) or placebo (N = 158). At the start of the treatment phase, the patients received initial doses of 400 mg or 600 mg dupilumab (arms with 200 mg or 300 mg dupilumab) or a corresponding placebo dose. During the entire treatment phase, continuation of the asthma maintenance treatment with ICS and LABA at a stable dose initiated before study inclusion was mandated. The use of as-needed medication was allowed in the study. Primary outcome was the change in the forced expiratory volume in 1 second (FEV1) at week 12. Study DRI12544 comprised a 2-week to 3-week screening phase, a 24-week treatment phase and a follow-up observation of 16 weeks. Further information on the DRI12544 study can be found in Table 9 and Table 10 in Appendix A of the full dossier assessment.

Study QUEST

The QUEST study is a randomized, double-blind, phase 3 study on the comparison of two different dupilumab dosages with placebo (1 placebo arm for each intervention arm). Patients 12 years of age and older with uncontrolled moderate to severe asthma who already received ongoing treatment with medium-dose or high-dose ICS and one or two further control medications (e.g. LABA) at a stable dosage were randomly assigned to the study. Moreover, the included patients had experienced worsening of their asthma within the last year before the start of the study, which was defined by ≥ 1 treatment with systemic steroids or hospitalization or emergency treatment due to a deterioration of their symptoms.

A total of 1902 patients were randomly (2:2:1:1) assigned to the study arms dupilumab 300 mg every two weeks (N = 633), dupilumab 200 mg every two weeks (N = 631), placebo for 300 mg dupilumab (N = 321) or placebo for 200 mg dupilumab (N = 317). At the start of the treatment phase, the patients received initial doses of 400 mg or 600 mg dupilumab (arm with 200 mg or 300 mg dupilumab) or a corresponding placebo dose. The patients were to continue the asthma medication at a stable dose already received before the start of the study at a stable dose. Inclusion of patients receiving OCS maintenance treatment was not allowed. The use of as-needed medication was possible in the study.

Primary outcomes of the study were the annual rate of severe exacerbations as well as a change in the FEV1 at week 12. The QUEST study comprised a screening phase of 3 to 5 weeks and a treatment phase of 52 weeks. After the treatment phase, patients were observed over 12 weeks or could be included in the non-controlled study TRAVERSE, in which all patients received treatment with dupilumab. Further information on the QUEST study can be found in Table 9 and Table 10 in Appendix A.

Subpopulations of the studies DRI12544 and QUEST considered by the company

Besides the respective placebo arms of the studies DRI12544 and QUEST, the company only considered those intervention arms for the benefit assessment in which patients received 200 mg dupilumab every 2 weeks in accordance with the approval. From these, the company considered those patients who had already received a high dose of ICS before being included in the study and who continued this therapy at a stable dose during the study. The subpopulations analysed by the company comprised 19.6% (DRI12544) or 25.7% (QUEST) of the total study population. The company provided no information on which ICS dose it regarded as high.

The company did not further limit the patient population according to type 2 inflammation criteria. The Summary of Product Characteristics (SPC) of dupilumab defines a type 2 inflammation as eosinophilia with ≥ 150 cells/µL and/or FeNO values ≥ 20 parts per billion (ppb) [19]. The company indicates that more than 90% (DRI12544) or 80% (QUEST) of the considered patients met the type 2 inflammation criteria. Apart from the missing information on the definition of a high ICS dose, the company's approach in the selection of the subpopulations is appropriate.

Study VENTURE

The VENTURE study is a randomized, double-blind phase 3 study on the comparison of dupilumab versus placebo in patients 12 years of age and older with uncontrolled severe asthma, who received ongoing asthma treatment with high-dose ICS and one or two further control medications at a stable dosage and who received regular treatment with OCS.

The patients included initially received either 600 mg followed by 300 mg dupilumab every 2 weeks (N = 103), or placebo (N = 107) in addition to their ongoing asthma treatment.

The effect of dupilumab on an intended dose reduction of the regularly administered OCS in comparison with placebo was the primary outcome investigated in the study. Randomization was preceded by a 3 to 8-week optimization phase during which the OCS dose was reduced in weekly steps using a prespecified titration scheme until the lowest effective dose was reached. No dose reduction was applied if the symptoms worsened (e.g. increase of the Asthma Control Questionnaire[ACQ]-5 value by ≥ 0.5 points compared to the previous measurement, occurrence of asthma exacerbation or a clinically relevant event).

Following the optimization phase, only those patients could be assigned to the two treatment arms who had been able to maintain their lowest effective OCS dose for two consecutive weeks prior to randomization. The treatment phase in which dupilumab or placebo was administered in addition to the ongoing asthma therapy was 24 weeks. Within these 24 weeks, the lowest effective OCS dose was initially maintained for 4 weeks, before the OCS dose was reduced every 4 weeks until week 20 according to a specified titration scheme under the condition that asthma control was maintained. The OCS dose was not to be adjusted in the last four weeks of the treatment phase. After the treatment phase, patients were observed over 12 weeks or were included in the non-controlled study TRAVERSE, in which all patients received treatment with dupilumab. Further information on the VENTURE study can be found in Table 9 and Table 10 in Appendix A of the full dossier assessment.

Patient populations of the VENTURE study considered by the company

The company used the total population of the VENTURE study for the benefit assessment. It justified this with the claim that all patients included had already received high ICS doses at baseline and that a total of 82% of the patient population had type 2 inflammation. This approach is adequate. Moreover, the company presented results of 2 subpopulations: patients with an eosinophil count of ≥ 150 cells/µL blood, as well as patients with a FeNO value of ≥ 25 ppb. The company did not use these results for the derivation of the added benefit of dupilumab.

ACT not implemented in the presented studies DRI12544, QUEST and VENTURE

The data presented from the DRI12544, QUEST and VENTURE studies are not suitable for assessing the added benefit of dupilumab in comparison with the ACT, as the various options for individual treatment escalation specified by the G-BA were not implemented. The patients in the studies DRI12544, QUEST and VENTURE considered by the company for the benefit assessment had inadequate asthma control with approx. 2 exacerbations in the previous year and an ACQ-5 value of 2 to 3 (average in each case). The treatment used before the start of the study was therefore inadequate to achieve the treatment goal of asthma control. In this situation, the guidelines recommend treatment escalation [3,20].

In the respective control arms, no treatment escalation was planned at the start of the study, whereas patients in the intervention arms received dupilumab as add-on therapy. According to the study planning, no treatment escalation was mandated in the framework of the concomitant treatment either. Instead, the ongoing asthma treatment administered prior to the screening was

to be continued at a stable dosage in all study arms (except for the OCS reduction in the VENTURE study). Sufficient information on the adjustments of the concomitant treatment during the studies is not available in the respective study documents. Overall, the ACT of an individual treatment escalation was not implemented in the studies DRI12544, QUEST and VENTURE.

This deviates from the assessment of the company, which regarded the ACT as implemented in the three studies presented. This assessment was inadequate. In the following, it will be discussed to what extent the individual treatment options of the ACT were implemented for the 3 studies presented by the company.

Treatment escalation with LAMA

Additional administration of LAMA such as tiotropium represents a possible treatment escalation within the ACT specified by the G-BA for patients receiving maintenance treatment with two control medications (e.g. ICS and LABA).

In DRI12544, all patients received only 2 control medications as concomitant medication at the start of the study: ICS and LABA. In the QUEST study, 57.6% of the patients in the control arm used by the company exclusively received ICS and LABA as concomitant medication at the start of the study. In the VENTURE study, 46% of the patients in the control arm received only 2 control medications (ICS and LABA) besides an OCS maintenance treatment at the start of the study. Taking into account the current clinical practice guidelines (CPGs) for asthma [3,20,21], treatment escalation with a third control medication with LAMA (e.g. tiotropium) is basically possible in all 3 studies. However, according to the study documents, initiation of a control medication with LAMA during the treatment phase was not possible in any of the studies. Within the framework of the ongoing maintenance treatment, the option of a therapy with LAMA was only exhausted in few patients. In the DRI12544 study, 2.6% of the patients received tiotropium as concomitant treatment. The data presented by the company provide no information on whether this proportion refers to the total population or to the subpopulation considered by the company. In the studies QUEST and VENTURE, approx. 10% and approx. 19% respectively of the patients considered by the company in the control arms continued their ongoing treatment with LAMA as second or third control medication. For the DRI12544 study, the company additionally noted that tiotropium had not been approved at the time the study started. Overall, LAMA was not available for the escalation of the ongoing treatment within the framework of the studies DRI12544, QUEST and VENTURE.

Regarding the studies DRI12544 and QUEST, the company provided no information on the extent to which it regarded a treatment escalation with LAMA as being implemented. For the VENTURE study, the company explained that, according to the guideline, an OCS maintenance treatment had to be performed as treatment of last choice. It can therefore be assumed that treatment with LAMA was not an option for those patients who did not receive concomitant treatment with LAMA in the study.

This assessment of the company is unjustified as the majority of patients in the VENTURE study had not been pretreated with LAMA and no data were available to document the unsuitability of LAMA.

Treatment escalation with omalizumab

According to the ACT specified by the G-BA, administration of omalizumab is another possibility of treatment escalation in immunoglobulin E [IgE]-mediated asthma, if the criteria of the approval and the note on treatment are fully met. The SPC names various criteria, such as reduced lung function, frequent symptoms during the day, nocturnal awakening and multiply documented severe asthma exacerbations [22].

Concomitant medication with omalizumab was not allowed in the studies DRI12544, QUEST and VENTURE; initiation of a therapy with omalizumab was ruled out. According to the exclusion criteria, patients who had received omalizumab within 130 days before the start of the study were not allowed to participate in the studies. This treatment option was thus not available for the patients included in the studies. Information on how many patients had already received omalizumab as prior therapy and for whom this drug was thus no longer available as treatment escalation, is missing for the studies DRI12544 and QUEST. The VENTURE study included no patients who had been pretreated with an anti-IgE antibody.

Nevertheless, it must be assumed that the three studies included a relevant number of patients for whom omalizumab was a suitable option for treatment escalation. According to the SPC, omalizumab can be administered from a baseline IgE of 30 IU/mL to 1500 IU/mL [22]. Based on the study documents for DRI12544, QUEST and VENTURE, it can be seen that more than 50% of the patients in the populations considered by the company in the control arms had a baseline IgE within these limits. However, it cannot be inferred from the study documents how many of the patients fully met the other criteria of the note on treatment [23] or of the approval besides the defined baseline IgE. According to the company's assessment, in contrast, omalizumab was only an option for a small proportion of patients in the therapeutic indication of dupilumab under consideration of the criteria mentioned in the treatment advice [23] and the body weight-dependent dosage [24]. This assessment was inadequate. It is assumed that a relevant number of patients considered by the company met both an appropriate IgE value and other criteria of the treatment advice (e.g. frequent symptoms, FEV1 $< 80\%$, ≥ 2 exacerbations within the last year) and were therefore eligible for treatment with omalizumab. The patient characteristics at the start of the study support this assessment. For instance, the average FEV1 values and the number of exacerbations corresponded to the data in the therapy note in all three studies.

According to the company, omalizumab had already been exhausted as a treatment option for the patients in the VENTURE study anyway, since the OCS maintenance treatment applied in all patients was to be performed as the last therapy option according to the current CPGs for asthma. This assessment of the company is inadequate because overall there is no information available on how far omalizumab is no longer an option for treatment escalation for these patients.

Treatment escalation with mepolizumab, reslizumab or benralizumab

Additional administration of mepolizumab, reslizumab or benralizumab is an option for individual treatment escalation in adults, provided that the criteria required for the application of the respective antibodies are met. The anti-IL-5 (receptor) antibodies mepolizumab, reslizumab and benralizumab are each approved for use in severe eosinophilic asthma [25-27]. According to the S2k guideline on the diagnosis and therapy of patients with asthma, the threshold value from which eosinophilia is considered manifest has not been conclusively clarified yet, but a threshold value of 150 eosinophils/µL is being discussed in this context [21].

Pretreatment and concomitant medication with biological drugs was generally prohibited in the studies DRI12544 and QUEST. According to the study protocol, mepolizumab and benralizumab were explicitly excluded as pre- and concomitant medications and were not available to patients as an option for treatment escalation in the VENTURE study. Nevertheless, it is assumed that the studies presented included a relevant number of patients for whom mepolizumab, reslizumab or benralizumab were suitable options for treatment escalation.

In the subpopulations considered by the company, for instance, 87% (DRI12544), 73% (QUEST) and 65% (VENTURE) of the patients in the respective control arms had more than 150 eosinophils/µL. The company itself presented this subpopulation (≥ 150 eosinophils/µL) from the VENTURE study for which the mentioned antibodies are an option according to the approval, in its dossier. Accordingly, the patient populations considered by the company in each study comprised a high proportion of patients with eosinophilic asthma for whom treatment escalation with mepolizumab, reslizumab or benralizumab was basically possible.

The company explained that mepolizumab, reslizumab and benralizumab had not been approved when the study was conducted and were not used in the studies. It also stated that a significant proportion of patients with severe uncontrolled asthma were not eligible for treatment with mepolizumab, reslizumab or benralizumab. It stated that treatment with these antibodies was not possible for patients without high eosinophil levels. This reasoning is inadequate and contradicts the subpopulation of patients with high eosinophil levels in the blood for whom treatment with anti-IL-5 (receptor) antibodies is basically possible presented by the company as supplementary information.

Summary

In the studies DRI12544, QUEST and VENTURE presented by the company, the patients included showed a need for treatment escalation. However, treatment optimization or escalation was excluded in the control arms of the presented studies. In fact, inadequate treatment that was ongoing before study inclusion was continued in the control arms. Hence, the ACT was not implemented in any of the studies presented. The effects observed in the studies DRI12544, QUEST and VENTURE thus permit no conclusion on the added benefit of dupilumab. There is no suitable information available on the extent to which the studies included patients for whom escalation of their existing asthma therapy was not an option and for whom the comparator therapy used in the studies thus represented the appropriate comparative therapy.

For the VENTURE study, it is overall questionable whether the applied therapy reflects the current therapy recommendations in the CPGs for asthma [3,20,21]. In contrast to the VENTURE study, guidelines state that OCS maintenance treatment as treatment escalation should only be performed when all of the above options have been exhausted, including LAMA, possibly omalizumab, and the anti-IL-5 (receptor) antibodies.

2.5.1 Results on added benefit

In its dossier, the company altogether presented no relevant data for the assessment of the added benefit of dupilumab as add-on maintenance treatment in adults with inadequately controlled severe type 2 inflammation asthma, who already receive high-dose ICS and at least one further drug as maintenance treatment, in comparison with the ACT. This resulted in no hint of an added benefit of dupilumab in comparison with the ACT; an added benefit is therefore not proven for this research question.

2.5.2 Probability and extent of added benefit

The data presented by the company for the assessment of the added benefit of dupilumab as add-on maintenance treatment in adults with inadequately controlled severe type 2 inflammation asthma who already receive high-dose ICS and at least one further drug as maintenance treatment are unsuitable for the derivation of an added benefit of dupilumab in comparison with the ACT. Hence, an added benefit of dupilumab is not proven for these patients.

This deviates from the assessment of the company, which derived proof of major added benefit for the joint patient population of adolescents and adults on the basis of the subpopulations of patients with high ICS doses from the studies DRI12544 and QUEST as well as of the total population of the VENTURE study used by it.

2.5.3 List of included studies

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

2.6 Probability and extent of added benefit – summary

Table 5 summarizes the result of the assessment of the added benefit of dupilumab in comparison with the ACT.

Table 5: Dupilumab – probability and extent of added benefit

Research question	Subindication	ACT[a]	Probability and extent of added benefit
1	Adolescents aged 12 to 17 years with inadequately controlled severe type 2 inflammation asthma[b], who already receive high-dose ICS and at least one further drug as maintenance treatment[c]	Individual treatment escalation[d] under consideration of the prior therapy choosing from: ▪ high-dose ICS and LABA and LAMA or ▪ high-dose ICS and LABA and possibly LAMA and omalizumab[e]	Added benefit not proven
2	Adults with inadequately controlled severe type 2 inflammation asthma[b], who already receive high-dose ICS and at least one further drug as maintenance treatment[c]	Individual treatment escalation[d] under consideration of the prior therapy and the pathogenesis of asthma choosing from: ▪ high-dose ICS and LABA and LAMA or ▪ high-dose ICS and LABA and possibly LAMA and omalizumab[e] or ▪ high-dose ICS and LABA and possibly LAMA and mepolizumab[e] or reslizumab[e] or benralizumab[e]	Added benefit not proven

a: Presentation of the ACT specified by the G-BA.
b: Characterized by an increased number of eosinophilic granulocytes and/or increased FeNO values.
c: Treatment with dupilumab was only indicated in addition to high-dose ICS and at least one further drug for maintenance treatment.
d: According to the G-BA, the step-by-step scheme for drug treatment of the NVL on asthma 2018 [3] was to be considered. It is assumed that in the therapeutic indication of dupilumab the patients of research question 1 are represented in steps 5 to 6 of the step-by-step scheme for drug treatment for children and adolescents, and the patients of research question 2 are represented in steps 4 to 5 of the step-by-step scheme for drug treatment for adults. The therapeutic indication also comprised patients for whom there was no further escalation option for their ongoing treatment.
e: As far as the criteria required for the application are met.
ACT: appropriate comparator therapy; FeNO: fractionated exhaled nitric oxide; G-BA: Federal Joint Committee; ICS: inhaled corticosteroid; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist; NVL: Nationale VersorgungsLeitlinie (National Care Guideline)

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

1. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10.07.2017 [Accessed: 04.06.2018]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2015; 58(1): 43-58.

3. Bundesärztekammer, Kassenärztliche Bundesvereinigung, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften. Nationale VersorgungsLeitlinie Asthma: Langfassung [online]. 2018 [Accessed: 23.10.2019]. URL: https://www.leitlinien.de/mdb/downloads/nvl/asthma/asthma-3aufl-vers1-lang.pdf.

4. Sanofi. An evaluation of dupilumab in patients with moderate to severe uncontrolled asthma [online]. In: ClinicalTrials.gov. 26.06.2017. URL: https://ClinicalTrials.gov/show/NCT01854047.

5. Sanofi-aventis Recherche et Développement. A randomized, double-blind, placebo-controlled, dose-ranging study to evaluate dupilumab in patients with moderate to severe uncontrolled asthma [online]. In: EU Clinical Trials Register. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2013-000856-16.

6. Wenzel S, Castro M, Corren J, Maspero J, Wang L, Zhang B et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting beta2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. Lancet 2016; 388(10039): 31-44.

7. Sanofi. A randomized, double-blind, placebo-controlled, dose-ranging study to evaluate dupilumab in patients with moderate to severe uncontrolled asthma: study DRI12544; clinical study report [unpublished]. 2016.

8. Sanofi. A randomized, double-blind, placebo-controlled, dose-ranging study to evaluate dupilumab in patients with moderate to severe uncontrolled asthma: study DRI12544; Zusatzanalysen [unpublished]. 2019.

9. Sanofi. Evaluation of dupilumab in patients with persistent asthma (liberty asthma quest) [online]. In: ClinicalTrials.gov. 23.10.2018. URL: https://ClinicalTrials.gov/show/NCT02414854.

10. Sanofi-aventis Recherche & Développement. A randomized, double blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of dupilumab in patients with persistent asthma [online]. In: EU Clinical Trials Register. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2014-004940-36.

11. Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. N Engl J Med 2018; 378(26): 2486-2496.

12. Sanofi. A randomized, double blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of dupilumab in patients with persistent asthma: study EFC13579; clinical study report [unpublished]. 2017.

13. Sanofi. A randomized, double blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of dupilumab in patients with persistent asthma: study EFC13579; Zusatzanalysen [unpublished]. 2019.

14. Sanofi. Evaluation of dupilumab in patients with severe steroid dependent asthma (venture) [online]. In: ClinicalTrials.gov. 23.10.2018. URL: https://ClinicalTrials.gov/show/NCT02528214.

15. Sanofi-aventis Recherche et Developpement. A randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of dupilumab in patients with severe steroid dependent asthma [online]. In: EU Clinical Trials Register. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-001573-40.

16. Rabe KF, Nair P, Brusselle G, Maspero JF, Castro M, Sher L et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. N Engl J Med 2018; 378(26): 2475-2485.

17. Sanofi. A randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of dupilumab in patients with severe steroid dependent asthma: study EFC13691; clinical study report [unpublished]. 2017.

18. Sanofi. A randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of dupilumab in patients with severe steroid dependent asthma: study EFC13691; Zusatzanalysen [unpublished]. 2019.

19. Sanofi Genzyme. Dupixent 200 mg Injektionslösung in einer Fertigspritze [online]. 08.2019 [Accessed: 10.10.2019]. URL: https://www.fachinfo.de/.

20. Global Initiative for Asthma. Global strategy for asthma management and prevention (2019 update) [online]. 2019 [Accessed: 23.10.2019]. URL: https://ginasthma.org/reports/.

21. Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin, Deutsche Atemwegsliga. S2k-Leitlinie zur Diagnostik und Therapie von Patienten mit Asthma: AWMF-Registernummer 020-009 [online]. 12.09.2017 [Accessed: 23.10.2019]. URL: https://www.awmf.org/uploads/tx_szleitlinien/020-009l_S2k_Asthma_Diagnostik_Therapie_2017-11_1.pdf.

22. Novartis Pharma. Xolair 150 mg Injektionslösung: Fachinformation [online]. 06.2019 [Accessed: 09.10.2019]. URL: https://www.fachinfo.de/.

23. Gemeinsamer Bundesausschuss. Anlage IV zum Abschnitt H der Arzneimittel-Richtlinie: Verordnungseinschrängkungen 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 [online]. 21.12.2016 [Accessed: 09.11.2017]. URL: https://www.g-ba.de/downloads/83-691-436/AM-RL-IV-Therapiehinweise_2016-12-21.pdf.

24. Novartis Europharm. Xolair 150 mg Injektionslösung. 01.2019.

25. GlaxoSmithKline. Nucala 100 mg Pulver zur Herstellung einer Injektionslösung: Fachinformation [online]. 08.2019 [Accessed: 09.10.2019]. URL: https://www.fachinfo.de/.

26. Teva. CINQAERO 10 mg/ml Konzentrat zur Herstellung einer Infusionslösung: Fachinformation [online]. 09.2018 [Accessed: 09.10.2019]. URL: https://www.fachinfo.de/.

27. AstraZeneca. Fasenra 30 mg Injektionslösung in einer Fertigspritze; Fasenra 30 mg Injektionslösung in einem Fertigpen: Fachinformation [online]. 06.2019 [Accessed: 09.10.2019]. URL: https://www.fachinfo.de/.

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a19-74-dupilumab-asthma-benefit-assessment-according-to-35a-social-code-book-v.12576.html.