IQWiG Reports – Commission No. A15-57

Tiotropium/olodaterol – Addendum to Commission A15-31[1]

Addendum

Commission: A15-57
Version: 1.0
Status: 14 January 2016

[1] Translation of addendum A15-57 *Tiotropium/Olodaterol – Addendum zum Auftrag A15-31* (Version 1.0; Status: 14 January 2016). 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:
Tiotropium/olodaterol – Addendum to Commission A15-31

Commissioning agency:
Federal Joint Committee

Commission awarded on:
22 December 2015

Internal Commission No.:
A15-57

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

IQWiG employees involved in the addendum[2]:

- Katrin Nink
- Lars Beckmann
- Petra Kohlepp
- Volker Vervölgyi

Keywords: tiotropium, olodaterol, pulmonary disease – chronic obstructive, benefit assessment

[2] Due to legal data protection regulations, employees have the right not to be named.

Table of contents

List of tables

Page

List of figures

Page

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AUC	area under the curve
CI	confidence interval
COPD	chronic obstructive pulmonary disease
EMA	European Medicines Agency
EQ-5D	European Quality of Life-5 Dimensions
FDA	Food and Drug Administration
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SGRQ	St. George's Respiratory Questionnaire
SMD	standardized mean difference
TDI	Transition Dyspnoea Index
VAS	visual analogue scale

1 Background

On 22 December 2015, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A15-31 (Tiotropium/olodaterol – Benefit assessment according to §35a Social Code Book (SGB) V [1]).

The 2 studies TONADO 1 and TONADO 2 on the comparison of tiotropium/olodaterol with tiotropium were included in dossier assessment A15-31. Subpopulations of both studies were relevant for the 2 research questions. Research question 1 comprises patients with chronic obstructive pulmonary disease (COPD) grade II and patients with COPD grades ≥ III with < 2 exacerbations per year. Research question 2 comprises patients with COPD grades ≥ III with ≥ 2 exacerbations per year. Treatment in both studies was conducted over a period of 52 weeks. Correspondingly, IQWiG's assessment was based on the data at the end of the study treatment after 52 weeks. In its dossier, the pharmaceutical company (hereinafter referred to as "the company") had also presented data at the time point after 24 weeks of treatment for individual outcomes. The G-BA commissioned IQWiG to assess the data of the studies TONADO 1 and TONADO 2 at the time point 24 weeks available in the company's dossier.

In the commenting procedure, the company, with its written comments, additionally submitted supplementary information to the G-BA for the proof of added benefit [2], which went beyond the information in the dossier [3]. In particular, these were data on health status (European Quality of Life-5 Dimensions visual analogue scale [EQ-5D VAS]), quality of life (St. George's Respiratory Questionnaire [SGRQ] responder) and data on study discontinuations due to adverse events (AEs). The G-BA's commission also included the assessment of these data subsequently submitted.

The responsibility for the present assessment and the results of the assessment lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Analyses at the time point 24 weeks

The randomized controlled trials TONADO 1 and TONADO 2 provided data for a treatment period of 52 weeks for all patient-relevant outcomes for the assessment. The company additionally presented data on the time point 24 weeks for individual outcomes. The analysis of the SGRQ total score at week 24 was the primary outcome according to the study report for a pooled analysis of both studies, which was performed in addition to the analysis of the individual studies. The responder analyses at the time point 24 weeks were planned as secondary outcome in this analysis, as were the pooled analyses on the Transition Dyspnoea Index (TDI) focal score. Analyses of the total score at the time point 52 weeks were also planned in the pooled analysis for both outcomes.

COPD is a chronic progressive disease. Symptom-relieving drugs such as the fixed combination tiotropium/olodaterol are indicated for maintenance treatment [4].

Concurring with the company's assessment, a minimum study duration of 24 weeks was determined for the present assessment. As described in the dossier assessment [1], this also complies with the assessment of the regulatory authorities European Medicines Agency (EMA) and Food and Drug Administration (FDA). Moreover, only studies with a minimum duration of one year can demonstrate maintenance of effect [5,6].

Hence the analyses for the longer period of 52 weeks were preferred in the IQWiG dossier assessment. Data at an earlier time point (24 weeks) may only contribute relevant information in this situation if they have a higher certainty of results. This was not the case in the present situation, however, so that the analyses at the time point 24 weeks, as presented in the dossier assessment, are not relevant for the present assessment. The available results at the time point 24 weeks are presented in Appendix A.

3 Assessment of the data subsequently submitted with the comment

3.1 Health status (EQ-5D VAS)

The company had presented no analyses on the outcome "health status (EQ-5D VAS) in its dossier, although the data had been recorded according to the study protocol.

3.1.1 Risk of bias

The company conducted no assessment of the risk of bias for the outcome "health status (EQ-5D VAS)" with its comment. Based on the available information, the risk of bias was rated as low.

3.1.2 Results (research question 1)

Table 1 presents the results on the comparison of tiotropium/olodaterol with tiotropium for patients of research question 1 (patients with COPD grade II and patients with COPD grades ≥ III with < 2 exacerbations per year) for the outcome "health status (EQ-5D VAS)".

Table 1: Results (health status EQ-5D VAS) at the time point 52 weeks – RCT, direct comparison: tiotropium/olodaterol vs. tiotropium (research question 1)

Outcome category Outcome Time point Study	Tiotropium/olodaterol		Tiotropium		Tiotropium/ olodaterol vs. tiotropium
	N[a]	Value at end of study mean[b] (SE)	N[a]	Value at end of study mean[b] (SE)	MD [95% CI][b]; p-value
Health status (EQ-5D VAS)[c]					
TONADO 1	222	72.21 (0.91)	259	71.32 (0.85)	0.89 [−1.55; 3.33]; ND
TONADO 2	237	71.04 (0.88)	237	68.24 (0.87)	2.80 [0.38; 5.23]; ND
Total					1.85 [−0.02; 3.72]; 0.052[d]

a: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study may be based on other patient numbers.
b: MMRM analysis of the FAS population.
c: The EQ-5D VAS records the self-reported current health status. The patients assess their health status on the VAS between 0 (worst imaginable health state) and 100 (best imaginable health state). Hence better (increasing) values indicate a better health status; positive effects in the group comparison (tiotropium/olodaterol – tiotropium) indicate an advantage of tiotropium/olodaterol.
d: Institute's calculation; meta-analysis with random effects according to DerSimonian and Laird.
CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; FAS: full analysis set; MD: mean difference; MMRM: mixed-effects model with repeated measures; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SE: standard error; VAS: visual analogue scale; vs.: versus

The meta-analysis of the included studies showed no statistically significant difference between the treatment groups for the outcome "health status (EQ-5D VAS)". This resulted in

no hint of an added benefit of tiotropium/olodaterol in comparison with tiotropium; an added benefit for health status (EQ-5D VAS) is therefore not proven.

3.1.3 Subgroups and other effect modifiers (research question 1)

As shown in the dossier assessment, only the results on subgroups and outcomes are presented in which the p-value of the interaction test was below the threshold value of 0.05. These were rated as indications of different subgroup effects. Hence, besides the results in the individual subgroups, the result of the total population was also considered in the interpretation of the results of these subgroup analyses, and the certainty of results was downgraded for conclusions based on subgroup analyses [1].

Table 2 presents the relevant results on subgroups for research question 1 (patients with COPD grade II and patients with COPD grades III and IV with fewer than 2 exacerbations per year).

Table 2: Subgroup "sex" (health status EQ-5D VAS) at the time point 52 weeks – RCT, direct comparison: tiotropium/olodaterol vs. tiotropium (research question 1)

Outcome Characteristic	Tiotropium/olodaterol		Tiotropium		Tiotropium/olodaterol vs. tiotropium
Study Subgroup	N[a]	Value at end of study mean[b] (SE)	N[a]	Value at end of study mean[b] (SE)	MD [95% CI]; p-value
Health status (EQ-5D VAS)[c]					
Sex					
TONADO 1					
Men	ND	ND	ND	ND	ND
Women	ND	ND	ND	ND	ND
TONADO 2					
Men	ND	ND	ND	ND	ND
Women	ND	ND	ND	ND	ND
Total				Interaction:	p-value = 0.044[d]
Men	328	70.92 (0.73)	355	70.37 (0.70)	0.56 [−1.43; 2.54]; ND Hedges' g: 0.04 [−0.11; 0.19][e]
Women	131	73.38 (1.24)	141	68.76 (1.23)	4.62 [1.20; 8.05]; ND Hedges' g: 0.32 [0.08; 0.56][e]

a: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study may be based on other patient numbers.
b: MMRM analysis of the FAS population.
c: The EQ-5D VAS records the self-reported current health status. The patients assess their health status on the VAS between 0 (worst imaginable health state) and 100 (best imaginable health state). Hence better (increasing) values indicate a better health status; positive effects in the group comparison (tiotropium/olodaterol – tiotropium) indicate an advantage of tiotropium/olodaterol.
d: Institute's calculation; meta-analysis with random effects according to DerSimonian and Laird.
e: Institute's calculation based on the changes at the end of the study (mean values and standard errors) of the MMRM.
CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; FAS: full analysis set; MD: mean difference; MMRM: mixed-effects model for repeated measures; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SE: standard error; VAS: visual analogue scale; vs.: versus

There was an indication of an effect modification regarding the characteristic "sex" for the outcome "health status (EQ-5D VAS)". A statistically significant advantage of tiotropium/ olodaterol in comparison with tiotropium was shown for women. For men, in contrast, no statistically significant difference between the treatment arms was identified.

The standardized mean difference (SMD) in the form of Hedges' g was considered to additionally check the relevance of the results in women. The 95% confidence interval (CI) of the SMD includes the irrelevance threshold of 0.2. It cannot be derived from this that the effect is relevant, and there is no hint of an added benefit of tiotropium/olodaterol in comparison with tiotropium for women. An added benefit for women is therefore not proven.

3.1.4 Results (research question 2)

The company submitted generally no additional data with its written comments for research question 2 and, in contrast to the dossier, described research question 2 as not relevant because the corresponding subpopulation could not be defined with sufficient clarity.

3.2 Health-related quality of life (SGRQ responder)

With its written comments, the company submitted 2 further analyses on the outcome "health-related quality of life (SGRQ)" for research question 1. The first one was an analysis of the time to first clinically relevant improvement of the SGRQ total score. The other analysis was a responder analysis investigating the total study period with an area under the curve (AUC), which is hereinafter referred to as "AUC analysis". The AUC analysis generally adopts a meaningful approach with regard to content.

The different analyses on health-related quality of life (prespecified and post hoc analyses on the SGRQ) are presented in Appendix A. These were the prespecified analyses presented by the company with the dossier (SGRQ total score and SGRQ responder) as well as the analyses subsequently submitted (SGRQ responder using the AUC analysis and analysis of the time to event).

The overall consideration of all analyses showed inconsistent results. Overall, the result of the original assessment was therefore not put into question by the analyses subsequently submitted.

3.3 Study discontinuations due to adverse events

Based on the information provided in the dossier, the outcome "discontinuation due to AEs" of the studies TONADO 1 and TONADO 2 was allocated to the outcome category "non-severe/non-serious AEs" in the dossier assessment A15-31 for the subpopulation of research question 1 (patients with COPD grade II and patients with COPD grade $\geq$ III with < 2 exacerbations per year). The fact that fewer than half of the discontinuations due to AEs were discontinuations due to serious AEs (42.7% in the tiotropium/olodaterol arm and 39.4% in the tiotropium arm) was decisive for this. However, these data were based on the discontinuations of the total study population as an auxiliary measure because the dossier contained no information on the number of discontinuations due to serious adverse events (SAEs) for the relevant subpopulations. The company subsequently submitted these data with its written comments.

The following Table 3 shows the proportions of the patients who discontinued the studies TONADO 1 and TONADO 2 due to SAEs.

Table 3: Results on the outcome "discontinuation due to AEs" – RCT, direct comparison: tiotropium/olodaterol vs. tiotropium (research question 1)

Outcome	Tiotropium/olodaterol		Tiotropium	
	N	Patients with event n (%)	N	Patients with event n (%)
Studies TONADO 1 and TONADO 2				
Discontinuation due to AEs	472	24 (5.1)	516	45 (8.7)
Discontinuation due to SAEs	472	14 (3.0)	516	24 (4.7)
AE: adverse event; N: number of analysed patients; n: number of patients with event; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus				

The information in Table 3 shows that patients who discontinued the study due to an AE, mostly discontinued the study due to SAEs (58.3% in the tiotropium/olodaterol arm and 53.3% in the tiotropium arm). The company's assessment that the outcome "discontinuation due to AEs" in the studies TONADO 1 and TONADO 2 for research question 1 is therefore to be allocated to the outcome category "serious/severe AEs" was therefore followed.

The company submitted no supplementary analyses on the discontinuations due to AEs for research question 2 (patients with COPD grades ≥ III with ≥ 2 exacerbations per year). Since no statistically significant difference between the treatment groups was shown for this subpopulation, however, a determination of the outcome category for research question 2 is also not required.

4 Extent and probability of the added benefit under consideration of the data subsequently submitted (research question 1)

The data presented in the dossier assessment together with the data submitted by the company in the written comments resulted in the following assessments for tiotropium/olodaterol in comparison with the appropriate comparator therapy (ACT) (tiotropium).

- Dossier assessment by IQWiG [1]:
  - an indication of an added benefit regarding COPD symptoms (TDI responder) for women
  - an indication of an added benefit regarding health-related quality of life (SGRQ responder) for women
- Additionally on the basis of the data subsequently submitted:
  - proof of an added benefit regarding discontinuations due to AEs for the total subpopulation

Table 4: Extent of added benefit at outcome level: tiotropium/olodaterol vs. tiotropium (research question 1: adult patients with COPD grade II and adult patients with COPD grade III and IV with < 2 exacerbations per year)

Outcome category **Outcome** **Characteristic**	**Tiotropium/olodaterol vs. tiotropium** **Proportion of events[a] or mean** **Effect estimate [95% CI]** **p-value** **Probability[b]**	**Derivation of extent[c]**
Mortality		
All-cause mortality	TIO/OLO: 1.2% to 1.7% TIO: 1.1% to 1.6% RR: 1.09 [0.38; 3.13] p = 0.868	Lesser benefit/added benefit not proven
Morbidity		
COPD symptoms (TDI responder)	TIO/OLO: 54.7% to 55.4% TIO: 47.0% to 52.8% RR: 1.10 [0.98; 1.25] p = 0.116	
Men	TIO/OLO: 52.3% TIO: 53.3% RR: 0.98 [0.85; 1.13] p = 0.808	Lesser benefit/added benefit not proven
Women	TIO/OLO: 61.7% TIO: 41.2% RR: 1.50 [1.17; 1.91] RR: 0.67 [0.52; 0.85][d] p = 0.001 probability: “indication”	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ added benefit, extent: “minor”
Exacerbations	TIO/OLO: 18.9% to 19.7% TIO: 20.6% to 22.7% RR: 0.89 [0.69; 1.14] p = 0.354	Lesser benefit/added benefit not proven
Severe exacerbations	Heterogeneous results without effects in the same direction[e]	Lesser benefit/added benefit not proven
Health status PGR[f]	Heterogeneous results without effects in the same direction[e]	
Men	TIO/OLO: 3.01 TIO: 3.05 MD: −0.04 [−0.19; 0.11] p = 0.601	Lesser benefit/added benefit not proven
Women	TIO/OLO: 2.76 TIO: 3.32 MD: −0.56 [−0.84; −0.28] SMD: −0.48 [−0.72; −0.24] p < 0.001	Lesser benefit/added benefit not proven[g]

(continued)

Table 4: Extent of added benefit at outcome level: tiotropium/olodaterol vs. tiotropium (research question 1: adult patients with COPD grade II and adult patients with COPD grade III and IV with < 2 exacerbations per year) (continued)

Outcome category **Outcome** **Characteristic**	**Tiotropium/olodaterol vs. tiotropium** **Proportion of events[a] or mean** **Effect estimate [95% CI]** **p-value** **Probability[b]**	**Derivation of extent[c]**
Health status EQ-5D VAS	TIO/OLO: 71.04 to 72.21 TIO: 68.24 to 71.32 MD: 1.85 [−0.02; 3.72] p = 0.052	
Men	TIO/OLO: 70.92 TIO: 70.37 MD: 0.56 [−1.43; 2.54] p = ND	Lesser benefit/added benefit not proven
Women	TIO/OLO: 73.38 TIO: 68.76 MD: 4.62 [1.20; 8.05] SMD: 0.32 [0.08; 0.56] p = ND	Lesser benefit/added benefit not proven[g]
Health-related quality of life		
SGRQ responder	TIO/OLO: 52.6% to 53.8% TIO: 49.8% to 49.8% RR: 1.07 [0.95; 1.21] p = 0.282	
Men	TIO/OLO: 50.3% TIO: 52.0% RR: 0.97 [0.83; 1.12] p = 0.665	Lesser benefit/added benefit not proven
Women	TIO/OLO: 60.3% TIO: 43.8% RR: 1.38 [1.08; 1.75] RR: 0.72 [0.57; 0.93][d] p = 0.009 probability: “indication”	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ added benefit, extent: “minor”

(continued)

Table 4: Extent of added benefit at outcome level: tiotropium/olodaterol vs. tiotropium (research question 1: adult patients with COPD grade II and adult patients with COPD grade III and IV with < 2 exacerbations per year) (continued)

Outcome category **Outcome** **Characteristic**	**Tiotropium/olodaterol vs. tiotropium** **Proportion of events[a] or mean** **Effect estimate [95% CI]** **p-value** **Probability[b]**	**Derivation of extent[c]**
Adverse events		
Serious adverse events	Heterogeneous results without effects in the same direction[e]	Greater/lesser harm not proven
Discontinuation due to AEs	TIO/OLO: 3.5% to 6.6% TIO: 6.8% to 10.7% RR: 0.58 [0.36; 0.93] p = 0.024 probability: "proof"	Outcome category: serious/severe AEs $0.90 \leq CI_u < 1.00$ added benefit, extent: "minor"

a: Minimum and maximum proportions of events in each treatment arm in the included studies.
b: Probability given if statistically significant differences are present.
c: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
d: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.
e: No common effect estimate provided due to heterogeneous data.
f: PGR indicates the health status on a scale from 1 (much better) to 4 (no change) to 7 (much worse).
g: A marginal effect cannot be excluded; an added benefit is not derived.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; COPD: chronic obstructive pulmonary disease; EQ-5D: European Quality of Life-5 Dimensions; MD: mean difference; ND: no data; OLO: olodaterol; PGR: patient global rating; RR: relative risk; SAE: serious adverse event; SGRQ: St. George's Respiratory Questionnaire; SMD: standardized mean difference; TDI: Transition Dyspnoea Index; TIO: tiotropium; VAS: visual analogue scale; vs.: versus

4.1 Overall conclusion on the added benefit (research question 1)

Table 5 summarizes the results that were considered in the overall conclusion on the added benefit from the dossier assessment together with the data presented by the company in the written comments.

Table 5: Positive and negative effects from the assessment of tiotropium/olodaterol compared with tiotropium (research question 1)

Positive effects	Negative effects
non-serious/non-severe symptoms/late complications ▪ TDI responder ▫ Sex women: indication of an added benefit – extent: "minor" men: lesser benefit/added benefit not proven Health-related quality of life ▪ SGRQ responder ▫ Sex women: indication of an added benefit – extent: "minor" men: lesser benefit/added benefit not proven Serious/severe adverse events ▪ Discontinuation due to AEs: proof of an added benefit – extent "minor"	–
AE: adverse event; SGRQ: St. George's Respiratory Questionnaire; TDI: Transition Dyspnoea Index	

Overall, only positive effects remain. Besides the positive effects for women for non-serious/non-severe symptoms/late complications (TDI responder) and health-related quality of life (SGRQ responder) presented already in the dossier assessment, proof of a minor added benefit for serious/severe AEs (discontinuation due to AEs) can additionally be derived on the basis of the data subsequently submitted. Overall, there is therefore proof of a minor added benefit of tiotropium/olodaterol in comparison with the ACT (tiotropium) for the total subpopulation of research question 1.

Summary

Table 6: Tiotropium/olodaterol: extent and probability of added benefit (research question 1)

Research question	Therapeutic indication	ACT[a]	Extent and probability of added benefit
1	Adult patients with COPD from moderate severity (50% ≤ FEV1 < 80% predicted)[b]	LABA (formoterol or salmeterol) and/or LAMA (**tiotropium**)	Proof of minor added benefit
a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold. b: For better understandability, the term "patients with COPD grade II and patients with COPD grades ≥ III with < 2 exacerbations per year" is used in the report. c: For better understandability, the term "patients with COPD grades ≥ III with ≥ 2 exacerbations per year" is used in the report. ACT: appropriate comparator therapy; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 second; G-BA: Federal Joint Committee; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist			

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

4.2 Overall conclusion on the added benefit (research question 2)

The company presented no additional data on research question 2 with its written comments. Hence there was no change for research question 2 regarding the added benefit in comparison with the dossier assessment [1].

5 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Tiotropium/Olodaterol: Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A15-31 [online]. 12 November 2015 [accessed: 4 January 2016]. (IQWiG-Berichte; Volume 337). URL: https://www.iqwig.de/download/A15-31_Tiotropium-Olodaterol_Nutzenbewertung-35a-SGB-V.pdf.

2. Boehringer Ingelheim. Stellungnahme zum IQWiG-Bericht Nr. 337: Tiotropium/Olodaterol; Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A15-31. [Soon available under: https://www.g-ba.de/informationen/nutzenbewertung/183/#tab/beschluesse in the document "Zusammenfassende Dokumentation"].

3. Boehringer Ingelheim Pharma. Tiotropium/Olodaterol (Spiolto Respimat): Dossier zur Nutzenbewertung gemäß § 35a SGB V; Modul 4 A; chronisch obstruktive Lungenerkrankung (COPD); medizinischer Nutzen und medizinischer Zusatznutzen, Patientengruppen mit therapeutisch bedeutsamen Zusatznutzen [online]. 13 August 2015 [accessed: 4 January 2016]. URL: https://www.g-ba.de/downloads/92-975-913/2015-08-13_Modul4A_TiotropiumOlodaterol.pdf.

4. Boehringer Ingelheim. Spiolto Respimat 2,5 Mikrogramm/2,5 Mikrogramm pro Hub Lösung zur Inhalation: Fachinformation [online]. July 2015 [accessed: 25 August 2015]. URL: http://www.fachinfo.de.

5. European Medicines Agency. Guideline on clinical investigation of medicinal products in the treatment of chronic obstructive pulmonary disease (COPD) [online]. 21 June 2012 [accessed: 30 September 2015]. URL: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/08/WC500130880.pdf.

6. Food and Drug Administration. Guidance for industry: chronic obstructive pulmonary disease; developing drugs for treatment; draft guidance [online]. November 2007 [accessed: 30 September 2015]. URL: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071575.pdf.

7. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555-574.

Appendix A – Results at the time point 24 weeks

A.1 – Research question 1

Table 7: Results (dichotomous outcomes) at the time point 24 weeks – RCT, direct comparison: tiotropium/olodaterol vs. tiotropium (research question 1)

Outcome category Outcome Study	Tiotropium/ olodaterol		Tiotropium		Tiotropium/olodaterol vs. tiotropium
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Mortality					
All-cause mortality	No data available				
Morbidity					
COPD symptoms (TDI responder)[a]					
TONADO 1	223	124 (55.6)	248	126 (50.8)	1.09 [0.92; 1.30][b]; ND
TONADO 2	233	130 (55.8)	236	119 (50.4)	1.11 [0.93; 1.31][b]; ND
Total					1.10 [0.98; 1.24]; 0.119[c]
Exacerbations[d]	No data available				
Severe exacerbations	No data available				
Health-related quality of life					
SGRQ responder[e]					
TONADO 1	221	140 (63.3)	247	114 (46.2)	1.37 [1.16; 1.62][c]; < 0.001[f]
TONADO 2	228	135 (59.2)	233	123 (52.8)	1.12 [0.95; 1.32][c]; 0.212[f]
Total			Heterogeneity: Q = 2.87; df = 1; p = 0.090; I^2 = 65.2%[c]		
Adverse events					
AEs	No data available				
Serious adverse events	No data available				
Discontinuation due to AEs	No data available				

a: Patients with TDI total score ≥ 1 point.
b: Calculated from GLM.
c: Institute's calculation; meta-analysis with random effects according to DerSimonian and Laird.
d: Includes moderate and severe exacerbations.
e: Patients with a reduction in the SGRQ total score of ≥ 4 points.
f: Institute's calculation, unconditional exact test (CSZ method according to Andrés [7]).

AE: adverse event; CI: confidence interval; COPD: chronic obstructive pulmonary disease; GLM: generalized linear model; N: number of analysed patients; n: number of patients with event; ND: no data; RCT: randomized controlled trial; RR: relative risk; SGRQ: St. George's Respiratory Questionnaire; TDI: Transition Dyspnoea Index; vs.: versus

Table 8: Results (continuous outcomes) at the time point 24 weeks – RCT, direct comparison: tiotropium/olodaterol vs. tiotropium (research question 1)

Outcome category Outcome Time point Study	Tiotropium/ olodaterol		Tiotropium		Tiotropium/ olodaterol vs. tiotropium
	N[a]	Value at end of study mean[b] (SE)	N[a]	Value at end of study mean[b] (SE)	MD [95% CI][b]; p-value
Morbidity					
Health status (PGR)[c]					
TONADO 1	226	2.99 (0.07)	257	3.21 (0.06)	−0.22 [−0.40; −0.04]; ND
TONADO 2	237	3.05 (0.07)	242	3.13 (0.07)	−0.08 [−0.26; 0.11]; ND
Total					−0.15 [−0.28; −0.01]; 0.032[d]
Health status (EQ-5D VAS)[e, f]					
TONADO 1	222	71.33 (0.89)	259	69.98 (0.84)	1.35 [−1.04; 3.75]; ND
TONADO 2	237	70.92 (0.86)	237	69.70 (0.85)	1.22 [−1.15; 3.59]; ND
Total					1.28 [−0.40; 2.97]; 0.135[d]

a: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study may be based on other patient numbers.
b: MMRM analysis of the FAS population.
c: PGR indicates the health status on a scale from 1 (much better) to 4 (no change) to 7 (much worse).
d: Institute's calculation; meta-analysis with random effects according to DerSimonian and Laird.
e: The EQ-5D VAS records the self-reported current health status. The patients assess their health status on the VAS between 0 (worst imaginable health state) and 100 (best imaginable health state). Hence better (increasing) values indicate a better health status; positive effects in the group comparison (tiotropium/olodaterol – tiotropium) indicate an advantage of tiotropium/olodaterol.
f: The company subsequently submitted the analyses on health status (EQ-5D VAS) with its written comments.
CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; FAS: full analysis set; MD: mean difference; MMRM: mixed-effects model with repeated measures; N: number of analysed patients; ND: no data; PGR: patient global rating; RCT: randomized controlled trial; SE: standard error; VAS: visual analogue scale; vs.: versus

A.2 – Research question 2

Table 9: Results (dichotomous outcomes) at the time point 24 weeks – RCT, direct comparison: tiotropium/olodaterol + ICS vs. tiotropium + ICS (research question 2)

Outcome category Outcome Study	Tiotropium/ olodaterol + ICS		Tiotropium + ICS		Tiotropium/olodaterol + ICS vs. tiotropium + ICS
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Mortality					
All-cause mortality	No data available				
Morbidity					
COPD symptoms (TDI responder)[a]					
TONADO 1	44	26 (59.1)	26	14 (53.8)	1.10 [0.71; 1.69][b]; ND
TONADO 2	28	15 (53.6)	38	20 (52.6)	1.02 [0.64; 1.61][b]; ND
Total					1.06 [0.77; 1.45]; 0.720[c]
Exacerbations[d]	No data available				
Severe exacerbations	No data available				
Health-related quality of life					
SGRQ responder[e]					
TONADO 1	43	24 (55.8)	24	9 (37.5)	1.49 [0.83; 2.66][b]; ND
TONADO 2	30	15 (50.0)	36	15 (41.7)	1.20 [0.71; 2.03][b]; ND
Total					1.32 [0.90; 1.95]; 0.160[c]
Adverse events					
AEs	No data available				
SAEs	No data available				
Discontinuation due to AEs	No data available				

a: Patients with TDI total score ≥ 1 point.
b: Calculated from GLM.
c: Institute's calculation; meta-analysis with random effects according to DerSimonian and Laird.
d: Includes moderate and severe exacerbations.
e: Patients with a reduction in the SGRQ total score of ≥ 4 points.

AE: adverse event; CI: confidence interval; COPD: chronic obstructive pulmonary disease; GLM: generalized linear model; ICS: inhaled corticosteroids; N: number of analysed patients; n: number of patients with event; ND: no data; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SGRQ: St. George's Respiratory Questionnaire; TDI: Transition Dyspnoea Index; vs.: versus

Table 10: Results (continuous outcomes) at the time point 24 weeks – RCT, direct comparison: tiotropium/olodaterol + ICS vs. tiotropium + ICS (research question 2)

Outcome category Outcome Study	Tiotropium/olodaterol + ICS		Tiotropium + ICS		Tiotropium/ olodaterol + ICS vs. tiotropium + ICS
	N[a]	Value at end of study mean[b] (SE)	N[a]	Value at end of study mean[b] (SE)	MD [95% CI][b]; p-value
Morbidity					
Health status (PGR)[c]					
TONADO 1	45	3.24 (0.17)	26	3.30 (0.23)	-0.06 [-0.62; 0.49]; ND Hedges' g: -0.06 [-0.54; 0.43][d]
TONADO 2	30	2.77 (0.22)	40	3.57 (0.19)	-0.80 [-1.38; -0.23]; ND Hedges' g: -0.66 [-1.14; -0.17][d]
Total			Heterogeneity: Q = 3.28; df = 1; p = 0.070; I^2 = 69.5%[e]		
Health status (EQ-5D VAS)	No data available				

a: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study may be based on other patient numbers.
b: MMRM analysis of the FAS population.
c: PGR indicates the health status on a scale from 1 (much better) to 4 (no change) to 7 (much worse).
d: Institute's calculation based on the changes at the end of the study (mean values and standard errors) of the MMRM.
e: Institute's calculation; meta-analysis with random effects according to DerSimonian and Laird.

CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; FAS: full analysis set; ICS: inhaled corticosteroids; MD: mean difference; MMRM: mixed-effects model with repeated measures; N: number of analysed patients; ND: no data; PGR: patient global rating; RCT: randomized controlled trial; SE: standard error; VAS: visual analogue scale; vs.: versus

A.3 – Subgroups and effect modifiers

Table 11: Subgroup "ethnicity" (health-related quality of life, SGRQ responder) at the time point 24 weeks – RCT, direct comparison: tiotropium/olodaterol vs. tiotropium (research question 2)

Outcome Characteristic Study Subgroup	Tiotropium/olodaterol		Tiotropium		Tiotropium/olodaterol vs. tiotropium	
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]	p-value
SGRQ responder[a]						
Ethnicity						
TONADO 1						
Men	ND	ND	ND	ND	ND	ND
Women	ND	ND	ND	ND	ND	ND
TONADO 2						
Men	ND	ND	ND	ND	ND	ND
Women	ND	ND	ND	ND	ND	ND
Total					Interaction:	0.034[b]
Caucasian	57	31 (54.4)	51	17 (33.3)	1.63 [1.03; 2.58]	0.030[c]
Non-Caucasian	15	8 (53.3)	8	6 (75.0)	0.71 [0.38; 1.32]	0.398[c]

a: Patients with a reduction in the SGRQ total score of ≥ 4 points.
b: Institute's calculation; meta-analysis with random effects according to DerSimonian and Laird.
c: Institute's calculation, unconditional exact test (CSZ method according to [7]).

CI: confidence interval; CSZ: convexity, symmetry, z score; N: number of analysed patients; n: number of patients with event; ND: no data; RCT: randomized controlled trial; RR: relative risk; SGRQ: St. George's Respiratory Questionnaire; vs.: versus

Appendix B – Results on health-related quality of life (SGRQ) – prespecified analyses and analyses subsequently submitted

Table 12: Results on health-related quality of life (SGRQ analyses) – RCT, direct comparison: tiotropium/olodaterol vs. tiotropium (research question 1)

Outcome category Outcome Time point Study	Tiotropium/olodaterol		Tiotropium		Tiotropium/ olodaterol vs. tiotropium
	N[a]	Value at end of study mean[b] (SE)	N[a]	Value at end of study mean[b] (SE)	MD [95% CI][b]; p-value
Health-related quality of life					
A priori analyses by the company in the dossier					
SGRQ total score					
Week 24					
TONADO 1	221	32.41 (0.78)	246	35.41 (0.74)	−3.00 [−5.11; −0.89]; ND Hedges' g: −0.26 [−0.44; −0.08][c]
TONADO 2	228	34.73 (0.81)	233	35.56 (0.79)	−0.83 [−3.05; 1.39]; ND Hedges' g: −0.07 [−0.25; 0.11][c]
Total			Heterogeneity: Q = 1.92; df = 1; p = 0.165; I^2 = 48.0%[d]		
Week 52					
TONADO 1	221	33.09 (0.88)	247	34.03 (0.83)	−0.94 [−3.31; 1.43]; ND
TONADO 2	228	34.58 (0.84)	233	36.14 (0.83)	−1.56 [−3.88; 0.77]; ND
Total					−1.25 [−2.91; 0.41]; 0.139[d]
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value**
SGRQ responder[e]					
Week 24					
TONADO 1	221	140 (63.3)	247	114 (46.2)	1.37 [1.16; 1.62][f]; < 0.001[g]
TONADO 2	228	135 (59.2)	233	123 (52.8)	1.12 [0.95; 1.32][f]; 0.212[g]
Total			Heterogeneity: Q = 2.87; df = 1; p = 0.090; I^2 = 65.2%[d]		
Week 52					
TONADO 1	221	119 (53.8)	247	123 (49.8)	1.08 [0.91; 1.29][f]; ND
TONADO 2	228	120 (52.6)	233	116 (49.8)	1.06 [0.89; 1.26][f]; ND
Total					1.07 [0.95; 1.21]; 0.282[d]

(continued)

Table 12: Results on health-related quality of life (SGRQ analyses) – RCT, direct comparison: tiotropium/olodaterol vs. tiotropium (research question 1) (continued)

Outcome Time point Study	Tiotropium/olodaterol		Tiotropium		Tiotropium/ olodaterol vs. tiotropium
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Analyses by the company subsequently submitted post-hoc with the comment					
SGRQ responder (AUC analysis)[e]					
Week 24	No data available				
Week 52					
TONADO 1	221	132 (59.7)	247	119 (48.2)	1.24 [1.05; 1.47][f]; ND
TONADO 2	228	138 (60.5)	233	128 (54.9)	1.10 [0.94; 1.29][f]; ND
Total					1.16 [1.04; 1.31]; 0.010[d]
	N	Time to event in days Q1 Patients with event n (%)	N	Time to event in days Q1 Patients with event n (%)	HR [95% CI]; p-value
Improvement SGRQ total score[e]					
Week 24	No data available				
Week 52					
TONADO 1	ND	ND	ND	ND	ND
TONADO 2	ND	ND	ND	ND	ND
Total	449	85 351 (78.2)	480	85 354 (73.8)	1.18 [1.02; 1.37]; 0.029

a: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study may be based on other patient numbers.
b: MMRM analysis of the FAS population.
c: Institute's calculation based on the changes at the end of the study (mean values and standard errors) of the MMRM.
d: Institute's calculation; meta-analysis with random effects according to DerSimonian and Laird.
e: Patients with a reduction in the SGRQ total score of ≥ 4 points.
f: Calculated from GLM.
g: Institute's calculation, unconditional exact test (CSZ method according to Andrés [7]).
AUC: area under the curve; CI: confidence interval; CSZ: convexity, symmetry, z score; FAS: full analysis set; GLM: generalized linear model; HR: hazard ratio; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; n: number of patients with event; ND: no data; Q1: lower quartile; RCT: randomized controlled trial; RR: relative risk; SE: standard error; SGRQ: St. George's Respiratory Questionnaire; vs.: versus

Appendix C – Presentation of the meta-analyses

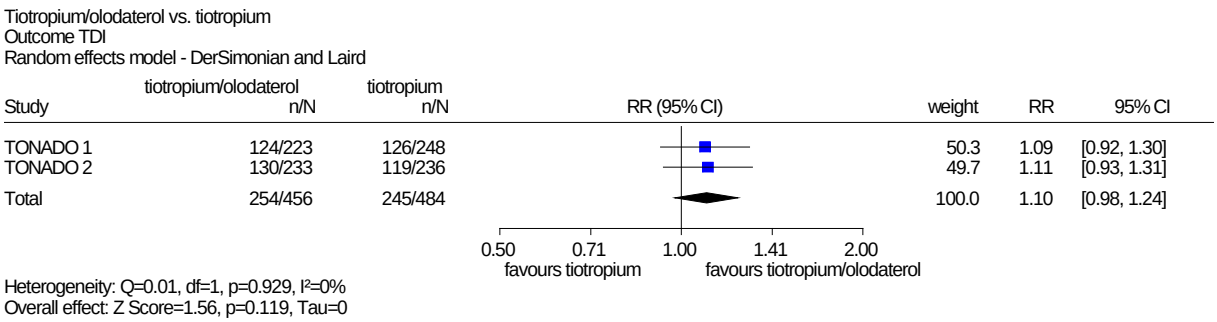

Figure 1: Meta-analysis, COPD symptoms at the time point 24 weeks (TDI responder), tiotropium/olodaterol vs. tiotropium, effect estimate: relative risk, Institute's calculation (research question 1)

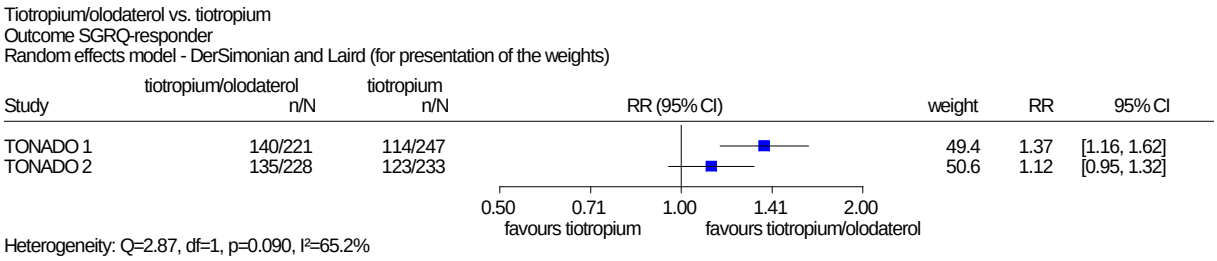

Figure 2: Meta-analysis, health-related quality of life at the time point 24 weeks (SGRQ responder), tiotropium/olodaterol vs. tiotropium, effect estimate: relative risk, Institute's calculation (research question 1)

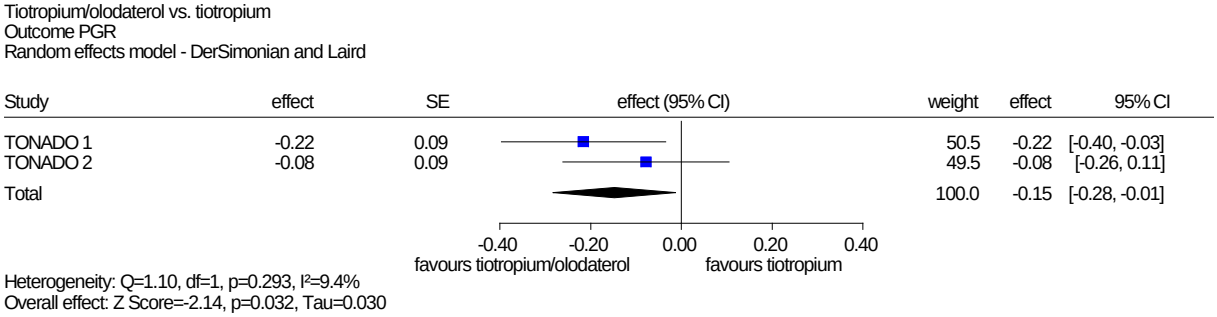

Figure 3: Meta-analysis, health status at the time point 24 weeks (patient global rating), tiotropium/olodaterol vs. tiotropium, effect estimate: mean difference, Institute's calculation (research question 1)

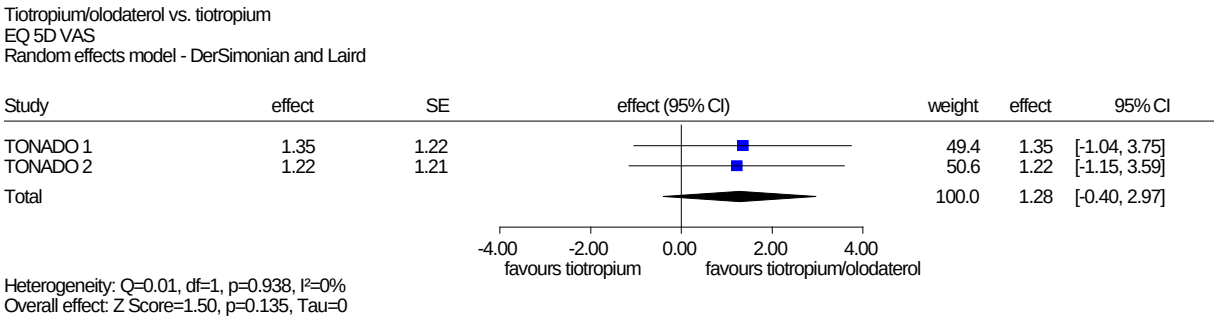

Figure 4: Meta-analysis, health status at the time point 24 weeks (patient global rating), tiotropium/olodaterol vs. tiotropium, effect estimate: mean difference, Institute's calculation (research question 1)

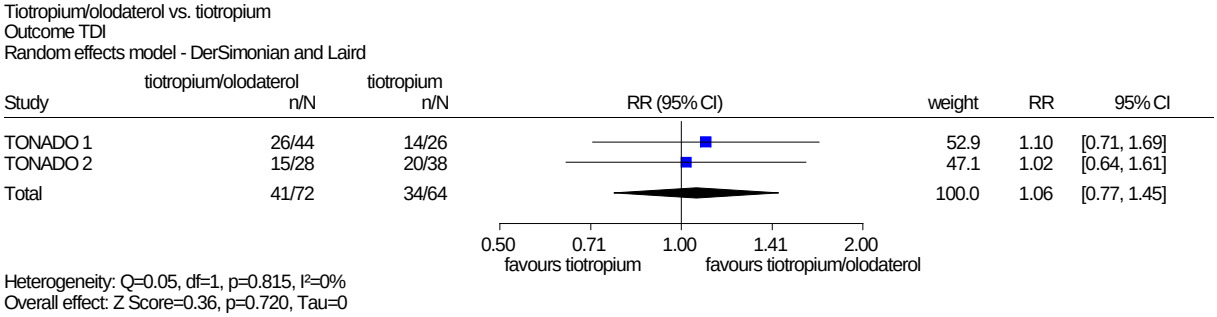

Figure 5: Meta-analysis, COPD symptoms at the time point 24 weeks (TDI responder), tiotropium/olodaterol vs. tiotropium, effect estimate: relative risk, Institute's calculation (research question 2)

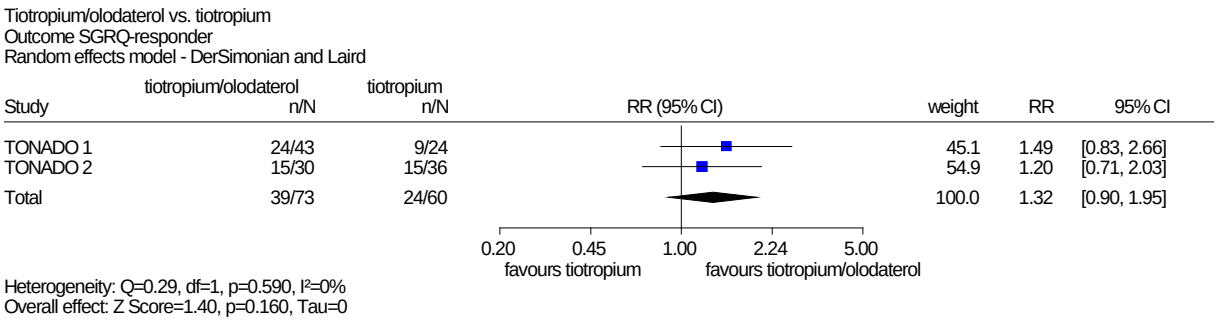

Figure 6: Meta-analysis, health-related quality of life at the time point 24 weeks (SGRQ responder), tiotropium/olodaterol vs. tiotropium, effect estimate: relative risk, Institute's calculation (research question 2)

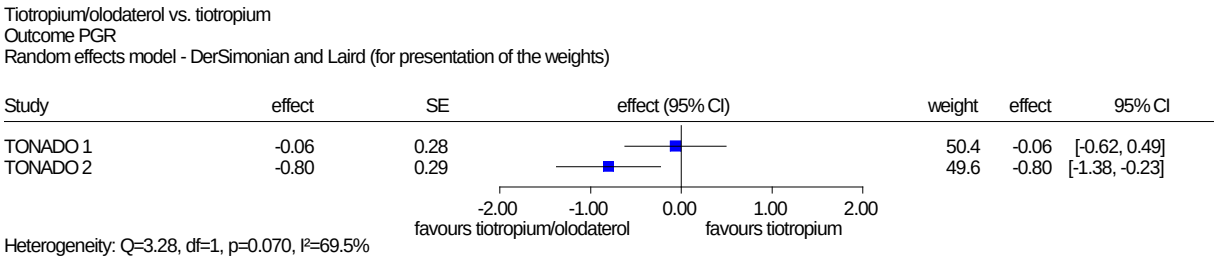

Figure 7: Meta-analysis, health status (patient global rating) at the time point 24 weeks, tiotropium/olodaterol vs. tiotropium, effect estimate: mean difference, Institute's calculation (research question 2)

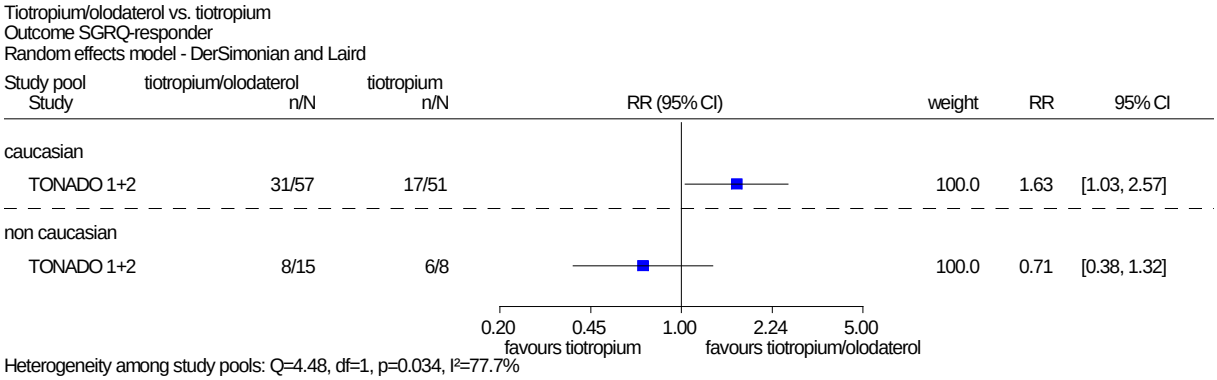

Figure 8: Meta-analysis, health-related quality of life at the time point 24 weeks (SGRQ responder), subgroup analysis (ethnicity) tiotropium/olodaterol vs. tiotropium, effect estimate: relative risk, Institute's calculation (research question 2)

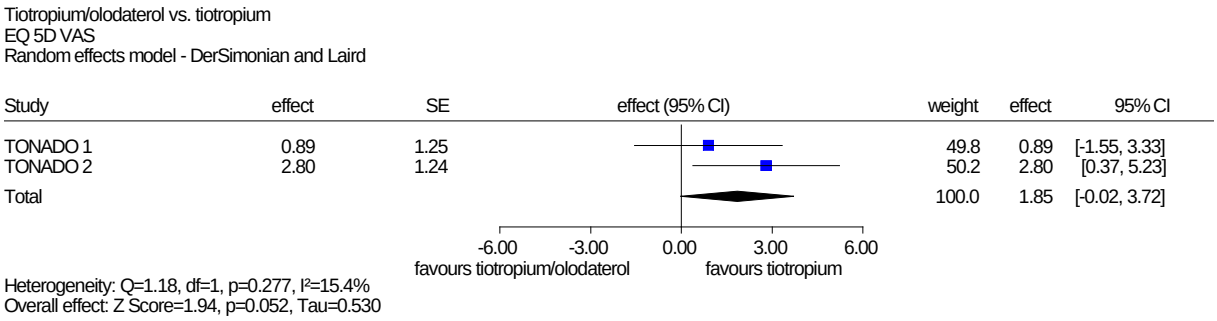

Figure 9: Meta-analysis, health status at the time point 52 weeks (EQ-5D VAS), tiotropium/olodaterol vs. tiotropium, effect estimate: mean difference, Institute's calculation (research question 1)

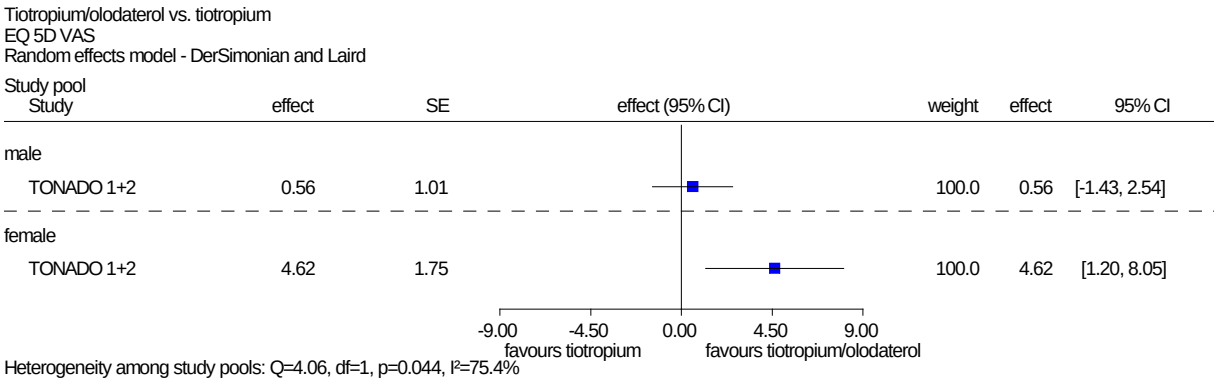

Figure 10: Meta-analysis, health status at the time point 52 weeks (EQ-5D VAS), subgroup analysis (sex), tiotropium/olodaterol vs. tiotropium, Institute's calculation (research question 1)

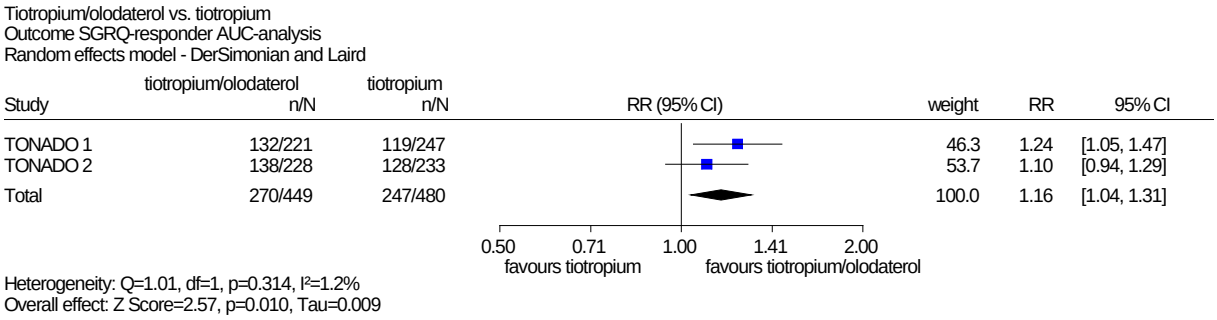

Figure 11: Meta-analysis, health-related quality of life at the time point 52 weeks (SGRQ responder, AUC analysis), tiotropium/olodaterol vs. tiotropium, effect estimate: relative risk, Institute's calculation (research question 1)