| Table S1 Inclusion criteria for studies for adjusted indirect comparison of vedolizumab *vs* adalimumab |
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|  |  | Inclusion criteria (studies not fulfilling these criteria were not eligible for inclusion) |
| I1 | Population  | Subpopulation 1: anti-TNF-α-naive patientsAdult patients with moderate to severe UC who have had inadequate response with, or lost response or were intolerant to conventional therapySubpopulation 2; anti-TNF-α-failure patients (not part of this manuscript)Adult patients with moderate to severe UC who have had inadequate response with, or lost response or were intolerant to anti-TNFα antibodyRationale: subpopulations defined in inclusion criteria 1 were predefined in VDZ label[21]  |
| I2 | Intervention | VDZ therapy had to adhere to recommended dosing regimen for UC treatment as per SMPC; recommended dose is 300 mg iv as initial dose, after 2 and 6 wk, and every 8 wk thereafter; ADA therapy1 had to adhere to recommended dosing regimen for UC as per SMPC; recommended dose is 160 mg sc at wk 0, 80 mg sc at wk 2 and thereafter 40 mg every other wk[21] Rationale: according to rules of procedure of the G-BA VerfO, early benefit assessment had to be based on label of intervention; therefore, label-conforming treatment of assessed therapy was required |
| I3 | Comparator therapy | Placebo or other common comparator2Rational: treatment with comparator had to be label conforming |
| I4 | Endpoints | ≥1 of following endpoints had to be reported in ≥1 relevant subpopulation:- Mortality- Morbidity (disease and therapy related)- Quality of lifeRationale: According to § 35 Section 1b Sentence 5 Social Code Book (SGB), § 5 Section 2 Sentence 3 AM-NutzenV and 5. Chapter, 2. Segment § 5 Section 2 Sentence 3 rules of procedure of the G-BA VerfO, aforementioned patient-relevant endpoints were acceptable |
| I5 | Study type | RCTsRationale: highest evidence level in clinical research is dedicated to RCT and systematic reviews on RCT (evidence classification see 2. Segment, 3. Section § 11 Section 3 VerfO). |
| E6 | Publication type | Original full text publication, study report, or detailed results reported in clinical study register; secondary publications without any additional relevant information were excluded from benefit assessment; studies only reported in congress abstracts or posters were excluded from assessment, as well, because information reported was considered insufficientRationale: evaluation of potential bias of study can only be done with sufficient information; this information can be deduced from original full text publication or clinical study report; detailed results report from clinical study register can be used in individual cases |
| I7 | Study duration | No restrictions |
| 1For evaluation of additional benefit compared with appropriate comparator therapy; 2For evaluation of additional benefit and for indirect comparison.ADA: Adalimumab; G-BA: Joint federal committee; G-BA VerfO: Rules of procedure of G-BA; RCT: Randomized controlled trial; SMPC: Summary of product characteristics; TNF: Tumor necrosis factor; UC: Ulcerative colitis; VDZ: Vedolizumab. |

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| **Table S2 Patient populations per endpoint** |
| **Study** | **Induction efficacy (wk 0- 6 [VDZ] or wk 8 [ADA])** | **Induction safety (wk 0-6 [VDZ] or wk 8 [ADA])** |
| **Efficacy population** | **Clinical remission** | **Clinical response** | **Mucosal healing** | **Safety population** | **AEs** | **Severe AEs** | **Serious AEs** | **AEs leading to discontinuation** | **Infections** |
| GEMINI 1 (NCT00783718)1  | Induction ITT-E: N=374Subpopulation of anti-TNF-α-naïve patients: 206 (55%) | VDZ q8wk: n=130placebo: n=76 | VDZ q8wk: n=130placebo: n=76 | VDZ q8wk: n=130placebo: n=76 | Induction safety population: N=895Subpopulation of anti-TNF-α-naïve patients: 464 (52%) | VDZ: n=388placebo: n=76 | VDZ: n=388placebo: n=76 | VDZ: n=388placebo: n=76 | VDZ: n=388placebo: n=76 | VDZ: n=388placebo: n=76 |
| ULTRA 1 (NCT00385736)2,3 | ITT: N=575Relevant treatment arms (ADA 160/80 mg or placebo): 445 (77%) | ADA 160/80 mg: n=223placebo: n=222 | ADA 160/80 mg: n=223placebo: n=222 | ADA 160/80 mg: n=223placebo: n=222 | Safety population: N=576 | ADA: n=353placebo: n=223 | ADA: n=353placebo: n=223 | ADA: n=353placebo: n=223 | ADA: n=353placebo: n=223 | ADA: n=353placebo: n=223 |
| ULTRA 2 (NCT00408629)3,4 | ITT: N=494Subpopulation of anti-TNF-α-naïve patients (ADA 160/80 mg or placebo): 295 (60%) | ADA 160/80 mg: n=150placebo: n=145 | ADA 160/80 mg: n=150placebo: n=145 | ADA 160/80 mg: n=150placebo: n=145 | Could not be included in analysis since safety data were not reported for anti-TNF-α-naïve patients separately (only full safety population) |
| M10-447 (NCT00853099)5,6 | ITT: N=273Relevant treatment arms (ADA 160/80 mg or placebo): 186 (68%) | ADA 160/80 mg: n=90placebo: n=96 | ADA 160/80 mg: n=90placebo: n=96 | ADA 160/80 mg: n=90placebo: n=96 | Safety population: N=273 | ADA: n=177placebo: n=96 | No data | ADA: n=177placebo: n=96 | ADA: n=177placebo: n=96 | ADA: n=177placebo: n=96 |
| Meta-analysis for ADA vs PCB | ULTRA 1 +ULTRA 2 +M10-447 | ADA 160/80 mg: n=463placebo: n=463 | ADA 160/80 mg: n=463placebo: n=463 | ADA 160/80 mg: n=463placebo: n=463 | ULTRA 1 +M10-447 | ADA: n=530placebo: n=319 | NA | ADA: n=530placebo: n=319 | ADA: n=530placebo: n=319 | ADA: n=530placebo: n=319 |
|  |
|  | **Maintenance efficacy (wk 6 [VDZ] or wk 8 [ADA]–wk 52)** | **Safety (wk 0–66 [VDZ; wk 52 + up to 14-wk follow-up] or wk 52 [ADA])** |
| **Study** | **Efficacy population** | **Clinical remission** | **Durable clinical remission** | **Corticosteroid-free remission** | **Clinical response** | **Mucosal healing** | **Durable clinical response** | **Safety population** | **AEs** | **Serious AEs** | **AEs leading to discontinuation** |
| GEMINI 1 (NCT00783718)[15]  | Maintenance ITT: N=373Subpopulation of anti-TNF-α-naïve patients: 224 (60%) | VDZ q8wk: n=72placebo: n=79 | VDZ q8wk: n=72placebo: n=79 | VDZ q8wk: n=39placebo: n=43 | VDZ q8wk: n=72placebo: n=79 | VDZ q8wk: n=72placebo: n=79 | VDZ q8wk: n=72placebo: n=79 | Maintenance safety population: N=895Subpopulation of anti-TNF-α-naïve patients: 464 (52%) | VDZ: n=309placebo: n=155 | VDZ: n=309placebo: n=155 | VDZ: n=309placebo: n=155 |
| ULTRA 1 NCT00385736)[13,17] | No clinical data on maintenance therapy with ADA available from ULTRA 1 trial since it was an induction study |
| ULTRA 2 (NCT00408629)[13,18] | ITT: N=494Relevant treatment arms (ADA 160/80 mg or placebo): 295 (60%) | ADA: n=891placebo: n=145 | ADA: n=150placebo: n=145 | ADA: n=692placebo: n=81 | ADA: n=89aplacebo: n=145 | ADA: n=891placebo: n=145 | ADA: n=150placebo: n=145 | Could not be included in analysis since safety data were not reported for anti-TNF-α-naïve patients separately (only full safety population) |
| M10-447 (NCT00853099)[20] | No ADA wk-8 responder data appropriate for indirect comparison were reported for maintenance phase in M10-447 | Safety population: N=362 | ADA: n=266placebo: n=96 | ADA: n=266placebo: n=96 | ADA: n=266placebo: n=96 |
| Meta-analysis for ADA vs placebo  | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| 1Data on wk-8 adalimumab (ADA) responders were included (response at wk 8 assessed by full Mayo Score); 2Data on wk-8 ADA responders who received corticosteroids at baseline were included (response at wk 8 assessed by full Mayo Score).AEs: Adverse events; f/u: Follow-up; ITT: Intention-to-treat; n: Patient number in study arm; N: Total patient number; NA: Not applicable; TNF: Tumor necrosis factor; VDZ: Vedolizumab. |

| **Table S3 Induction and maintenance efficacy results for adalimumab *vs* placebo in biologic-naïve patients with moderate to severe ulcerative colitis: individual study results from ULTRA 1[13], ULTRA 2[13,18], and M10-447[20], and meta-analysis results (if applicable)** |
| --- |
|  | **Induction phase (wk 0-8)** | **Maintenance phase(wk 8-52)1** |
| **RCT** | Placebo**n/N (%)** | ADA 160/80 mg**n/N (%)** | **RR (95 % CI)** | Placebo**n/N (%)** | ADA 40 mg every other wk**n/N (%)** | **RR (95 % CI)** |
| **Patients in clinical remission** |
| ULTRA 1 | 16/222 (7) | 35/223 (16) | 2.18 (1.24-3.82) | NA (induction trial) |
| ULTRA 2 | 16/145 (11) | 32/150 (21) | 1.93 (1.11-3.37) | 18/145 (12) | 28/89 (31) | 2.53 (1.49-4.31) |
| M10-447 | 11/96 (11) | 9/90 (10) | 0.87 (0.38-2.01) | NA (no wk-8 responder data available) |
| Meta-analysis | 43/463 (9) | 76/463 (16) | 1.68 (1.04-2.71)2 | NA |
| **Patients with clinical response**  |
| ULTRA 1 | 95/222 (43) | 116/223 (52) | 1.22 (1.00-1.48) | NA (induction trial) |
| ULTRA 2 | 56/145 (39) | 89/150 (59) | 1.54 (1.20-1.96) | 35/145 (24) | 44/89 (49) | 2.05 (1.43-2.93) |
| M10-447 | 34/96 (35) | 45/90 (50) | 1.41 (1.00-1.98) | NA (no wk-8 responder data available) |
| Meta-analysis | 185/463 (40) | 250/463 (54) | 1.35 (1.16-1.57)2 | NA |
| **Patients with mucosal healing**  |
| ULTRA 1 | 79/222 (36) | 99/223 (44) | 1.25 (0.99-1.57) | NA (induction trial) |
| ULTRA 2 | 51/145 (35) | 74/150 (49) | 1.40 (1.07-1.84) | 28/145 (19) | 40/89 (45) | 2.33 (1.55-3.49) |
| M10-447 | 29/96 (30) | 40/90 (44) | 1.47 (1.00-2.16) | NA (no wk-8 responder data available) |
| Meta-analysis | 159/463 (34) | 213/463 (46) | 1.34 (1.14-1.57)2 | NA |
| **Patients in durable clinical remission3** |
| ULTRA 2 | NA | 9/145 (6) | 16/150 (11) | 1.72 (0.78-3.76) |
| **Patients in corticosteroid-free clinical remission4** |
| ULTRA 2 | NA | 5/81 (6) | 14/69(20) | 3.29 (1.25-8.67) |
| **Patients with durable clinical responsec** |
| ULTRA 2 | NA | 24/145 (17) | 44/150 (29) | 1.77 (1.14-2.76) |
| 1Patients who had responded to induction treatment at wk 8 (adalimumab [ADA]; assessed per partial Mayo score) for all endpoints except durable clinical remission and durable clinical response; in ULTRA 2, wk-8 responder data were available for ADA, but not placebo group; therefore, data from patients randomized to placebo in ULTRA 2 were included in analysis irrespective of wk-8 responder status; this is a conservative approach that presents greater deltas between ADA and placebo arms and, consequently, overestimation of treatment effect differences between the 2 arms; 2Meta-analyzed data from ULTRA 1, ULTRA 2, and M10-447; heterogeneity tests: I²=41%; p=0.18 (clinical remission); I²=10%; p=0.33 (clinical response); I²=0%; p=0.70 (mucosal healing); 3Endpoint definitions for durable clinical remission and durable clinical response reflect remission/response after induction (wk 6/8) and at wk 52: while in GEMINI 1, these endpoints were analyzed in maintenance intent-to-treat (vedolizumab q8wk) population, thus capturing induction response at wk 6 as prerequisite for randomization to maintenance phase, durable clinical remission and durable clinical response rates from ULTRA 2 refer to patient numbers at randomization (wk 0); 4Anti-tumor necrosis factor-α-naïve patients with concomitant corticosteroids at baseline: ULTRA 2: 69 patients randomized to ADA who were assessed as wk-8 responders and 81 randomized to placebo (wk-8 response status not reported; therefore, all placebo patients on concomitant corticosteroids included in analysis). CI: Cconfidence interval; n: Number of patients who achieved the outcome; N: Number of patients evaluated; NA: Not applicable; RCT: Randomized controlled trial; RR: Relative risk. |

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| **Table S4 Induction and maintenance safety results for adalimumab *vs* placebo in biologic-naïve patients with moderate to severe ulcerative colitis: individual study results from ULTRA-1[17] and M10-447[20], and meta-analysis results (if applicable)**

|  |  |  |
| --- | --- | --- |
|  | Induction phase (wk 0-8) | Overall study(wk 0-52) |
| Clinical endpoint | RCT | Placebon/N (%) | ADA1n/N (%) | RR (95 % CI) | Placebon/N ( %) | ADA1n/N (%) | RR (95% CI) |
| AE | ULTRA 1 | 108/223 (48) | 182/353 (52) | 1.06 (0.90-1.26) | NA (induction trial) |
| M10-447 | 45/96 (47) | 89/177 (50) | 1.07 (0.83-1.39) | 67/96 (70) | 261/266 (98) | 1.41 (1.23-1.61) |
| Meta-analysis | 153/319 (48) | 271/530 (51) | 1.07 (0.93-1.23)2 | NA |
| Severe AE3 | ULTRA-1 | 17/223 (8) | 28/353 (8) | 1.04 (0.58-1.86) | NA (induction trial) |
| Serious AE | ULTRA 1 | 17/223 (8) | 14/353 (4) | 0.52 (0.26-1.03) | NA (induction trial) |
| M10-447 | 7/96 (7) | 6/177 (3) | 0.46 (0.16-1.34) | 12/96 (12) | 90/266 (34) | 2.71 (1.55-4.72) |
| Meta-analysis | 24/319 (8) | 20/530 (4) | 0.50 (0.28-0.90)2 | NA |
| AE leading to discontinuation | ULTRA 1 | 12/223 (5) | 20/353 (6) | 1.05 (0.53-2.11) | NA (induction trial) |
| M10-447 | 4/96 (4) | 6/177 (3) | 0.81 (0.24-2.81) | 5/96 (5) | 37/266 (14) | 2.67 (1.08-6.60) |
| Meta-analysis | 16/319 (5) | 26/530 (5) | 0.99 (0.54-1.82)2 | NA |
| ≥1 infection | ULTRA 1 | 35/223 (16) | 58/353 (16) | 1.05 (0.71-1.54) | NA (induction trial) |
| M10-447 | 15/96 (16) | 28/177 (16) | 1.01 (0.57-1.80) | NA (not reported) |
| Meta-analysis | 50/319 (16) | 86/530 (16) | 1.04 (0.75-1.43)2 | NA |
| 1All adalimumab (ADA)-treated patients were included in safety analysis, including randomized and open-label treated patients, 160/80- and 80/40-mg induction, as well as maintenance every other wk or qwk dosing; 2Meta-analyzed data from ULTRA 1 and M10-447: heterogeneity tests: I²=0 %, p=0.96 (adverse event [AE]); I²=0 %, p=0.86 (serious AE); I²=0 %, p=0.72 (AE leading to discontinuation); I²=0%, p=0.92 (infection); 3Defined as AE of severe intensity by investigator according to criteria of “inability to perform normal daily activities.”CI: Confidence interval; n: Number of patients with events; N: Number of patients evaluated; NA: Not applicable; RCT: Randomized controlled trial; RR: Relative risk.Data source:ULTRA-1: Reinisch W et al. *Gut.* 2011;60:780-7. M10-447: Suzuki Y et al. *J Gastroenterol.* 2014;49:283-94 and study results entry from clinicaltrials.gov NCT00853009, available at <https://www.clinicaltrials.gov/ct2/show/results/NCT00853099?term=NCT00853099&rank=1> |

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Systematic bibliographic

literature search in May 2014

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| **Vedolizumab**Cochrane n=8Embase n=416MEDLINE n=56**Results n=480** | **Adalimumab**Cochrane n=9Embase n=521MEDLINE n=29**Results n=559** |

Title/abstract screening

|  |  |
| --- | --- |
| **Vedolizumab****n=425** | **Adalimumab****n=521** |

Automatically removed duplicates

|  |  |
| --- | --- |
| **Vedolizumab****n=55** | **Adalimumab****n=38** |

Full text screening

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| --- | --- |
| **Vedolizumab****n=2** | **Adalimumab****n=6** |

Not relevant

|  |  |
| --- | --- |
| **Vedolizumab****n=423** | **Adalimumab****n=515** |

Not relevant

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| --- | --- |
| **Vedolizumab****n=1** | **Adalimumab****n=1** |

Exclusion criteria.

Not RCT

Relevant

|  |  |
| --- | --- |
| **Vedolizumab**Publication**n=1**Studies**n=1****(GEMINI 1)** | **Adalimumab**Publication**n=5**Studies **n=3** **(ULTRA 1, ULTRA 2, M10-447)** |

Figure S1. Flow chart for bibliographic literature search for randomized controlled trials (RCTs) investigating vedolizumab or adalimumab