HTA CG | MEMBER STATE COORDINATION GROUP ON HEALTH TECHNOLOGY ASSESSMENT

Annex 1 to Guidance on filling in the JCA dossier template – Medicinal products
Table template collection – Filled-in examples

V1.0

8 October 2024

Adopted on 28 November 2024 by the HTA CG pursuant to Article 3(7), point (d), of Regulation (EU) 2021/2282 on Health Technology Assessment

The collection of empty tables is a supplement to the guidance on filling in the joint clinical assessment (JCA) dossier template to provide further details to support data presentation. HTDs select the appropriate tables taking into account the type of information, study or data to be presented. Tables may be adapted according to the specific requirements of the data and analyses to be presented.

This document includes filled-in examples of tables from the table template collection.

Table 1: Studies performed or sponsored by the HTD in the therapeutic indication for which the dossier is prepared

Study reference/ID	**Study for marketing authorization of the medicinal product under assessment**	**Study status**	**Study duration** **Data cut-off, if applicable**	**Study arms**
JA0010EN3001 (CLINEVID 1[a])	no	completed	14 months Data cut-off at week 24: 03.08.2020	Intervention: ▪ A-mab 100 mg (Q8W) Comparator: ▪ Placebo
JA0010EN3002 (CLINEVID 2[a])	yes	completed	15 months Data cut-off at week 24: 14.03.2019 safety data cut-off: 01.05.2019	Intervention: ▪ A-mab 100 mg (Q4W) ▪ A-mab 100 mg (Q8W) Comparator: ▪ Placebo
JA0010EN3003 (CLINEVID 3[a])	yes	completed	28 months Data cut-off at week 24: 06.03.2019 safety data cut-off: 01.05.2019	Intervention: ▪ A-mab 100 mg (Q4W) ▪ A-mab 100 mg (Q8W) Comparator: ▪ Placebo
JA0010EN3004 (CLINEVID 4[a])	no	completed	15 months Data cut-off at week 24: 21.03.2012	Intervention: ▪ B-mab 45 mg (Q12W) ▪ B-mab 90 mg (Q12W) Comparator: ▪ Placebo
a: in the following tables, the study is referred to with this abbreviated form				
HTD: health technology developer; Q2W: once every two weeks; Q4W: once every 4 weeks; Q8W: once every 8 weeks; Q12W: once every 12 weeks				

Table 2: Studies performed or sponsored by the HTD in the therapeutic indication for which the dossier is prepared and which are excluded

Study reference/ID	**Reasons for study exclusion**
CLINEVID 2	Comparator (placebo), population (biologically naïve patients)
HTD: health technology developer	

Table 4: Relevant studies from the search in bibliographic databases

Study reference/ID	**Reference**
CLINEVID 5	Mueller C. et al. 2018 [1], Mueller J. et al. 2019 [2], Mueller H. et al. 2020 [3], Mueller I. et al. 2019 [4]

Study reference/ID	Reference
CLINEVID 6	Mueller C. et al. 2018 [1], Mueller J. et al. 2019 [2], Mueller H. et al. 2020 [3], Mueller I. et al. 2019 [4], Mueller G. et al. 2017 [5]
CLINEVID 1	Mueller B. et al. 2022 [6]
CLINEVID 2	Mueller A. et al. 2020 [7]
CLINEVID 4	Mueller F. et al. 2016 [8], Mueller E. et al. 2014 [9], Mueller D. et al. 2016 [10]

Table 5: Relevant studies from the search in study registries

Study reference/ID	Identification locations (Name of the study registry and references[a])	Study included in the study list of the HTD (yes/no)	Study identified based on search in bibliographic databases (yes/no)	Status (completed/ discontinued/ ongoing
CLINEVID 5	NCT02207213 [11] EudraCT 2014-000719-51 [12]	yes	yes	completed
CLINEVID 6	NCT02207442 [13] EudraCT 2014-000720-81 [14]	yes	yes	completed
CLINEVID 1	NCT03796885 [15] EudraCT 2018-003214-14 [16]	yes	yes	completed
CLINEVID 2	NCT03162769 [17] EudraCT 2016-001163-73 [18]	yes	yes	completed
CLINEVID 4	NCT01077326 [19] EudraCT 2009-012265-06 [20]	yes	yes	completed
a: reference of the study registry entry, number (NCT-Number, EudraCT-Number) and, if available, reference of the reports on study design and/or results listed in the study registry				
HTD: health technology developer				

Table 7: HTA reports on the medicinal product subject to the JCA in the indication under assessment

HTA report title	Country affiliation	*Reference*
A-mab (Psoriasis-Arthritis) – Nutzenbewertung gemäß § 35a SGB V	Germany	[21]
CADTH Reimbursement Review A-mab (Psorya)	Canada	[22]
…		
CADTH: Canadian Agency for Drugs and Technology in Health		

Table 8: Studies from submission files to the EMA

Studies included in the JCA	Applicable PICO question
CLINEVID 5[a]	PICO 1
CLINEVID 6[a]	PICO 1

Studies included in the JCA	**Applicable PICO question**
CLINEVID 2[b]	PICO 2
CLINEVID 4[c]	PICO 2
Studies not included in the JCA	**Reasons for study exclusion**
CLINEVID 3[b]	Comparator (placebo), population (biologically naïve patients)
a: marketing authorization studies of A-mab in the indication plaque psoriasis b: marketing authorization studies of A-mab in the indication psoriatic arthritis c: marketing authorization study of B-mab in the indication psoriatic arthritis	

Table 9: Included studies – list of relevant studies by PICO question

Study reference/ID **Study type** **Study interventions**	**Study for marketing authorization***	**Sponsored[a] or third-party study of the medicinal product under assessment**	**Available documentation in the submission dossier**
PICO 1 (adult patients with active psoriatic arthritis, who have had an inadequate response to prior DMARD therapy)			
Studies providing direct evidence A-mab vs. C-mab			
CLINEVID 5 RCT: A-mab vs. C-mab	yes[b]	sponsored	▪ CSR: [23] ▪ Registry entry[c]: NCT02207213 [11],EudraCT 2014-000719-51 [12] ▪ Publication or other reference: [1-4]
CLINEVID 6 RCT: A-mab vs. C-mab	yes[b]	sponsored	▪ CSR: [24] ▪ Registry entry[c]: NCT02207422 [13], EudraCT 2014-000720-81 [14] ▪ Publication or other reference: [1-5]
PICO 2 (adult patients with active psoriatic arthritis, who have had an inadequate response to prior bDMARD therapy)			
Studies providing indirect evidence A-mab vs. B-mab			
CLINEVID 1 RCT: A-mab vs. Placebo	no	sponsored	▪ CSR: [25] ▪ Registry entry[c]: NCT03796885 [15], EudraCT 2018-003214-14 [16] ▪ Publication or other reference: [6]
CLINEVID 2 RCT: A-mab vs. Placebo	yes[d]	sponsored	▪ CSR: [26] ▪ Registry entry[c]: NCT03162769 [17], EudraCT 2016-001163-73 [18] ▪ Publication or other reference: [7]
CLINEVID 4 RCT: B-mab vs. Placebo	yes[e]	sponsored	▪ CSR: [27] ▪ Registry entry[c]: NCT01077326 [19], EudraCT 2009-012265-06 [20] ▪ Publication or other reference: [8-10]

Study reference/ID **Study type** **Study interventions**	**Study for marketing authorization***	**Sponsored[a] or third-party study of the medicinal product under assessment**	**Available documentation in the submission dossier**
* if yes, please provide information such as date and commission implementing decision in footnote a: study sponsored by the HTD or in which the HTD participated financially in some other way b: marketing authorisation of A-mab in the therapeutic indication of plaque psoriasis (Commission Implementing Decision 2017/7694 of 10.11.2017) c: study registry entry, number (NCT-Number, EudraCT-Number) d: variation to the existing marketing authorisation of A-mab to include psoriasis arthritis as new therapeutic indication (Commission Implementing Decision 2020/8229 of 20.11.2020) e: variation to the existing marketing authorisation of B-mab to include psoriasis arthritis as new therapeutic indication (Commission Implementing Decision 2013/6602 of 19.09.2013)			
bDMARD: biologic disease modifying antirheumatic drug; CSR: clinical study report; DMARD: disease modifying antirheumatic drug; HTD: health technology developer; RCT: randomised controlled trial			

Table 10: Characteristics of the included studies

Study reference/ID	**Study type and design**	**Study population**	**Study arms (number of randomised/included patients)**	**Study duration, data cut off(s) and locations**	**Study endpoints**
CLINEVID 1	RCT, double-blind, parallel	Adults with active psoriatic arthritis[a] who have had an inadequate response or who have been intolerant to 1 or 2 prior therapies with TNF inhibitors	A-mab (N = 189) Placebo (N = 96)	▪ Study duration: ▫ Screening: up to 6 weeks ▫ Treatment: 48 weeks (placebo arm: switch to A-mab after 24 weeks) ▫ Follow-up: 8 weeks (safety) ▪ Period of study: 3/2019–11/2021 ▪ Data cut-off at week 24[b]: 3 August 2020 ▪ 84 centres in Asia (23) and Europe (61)	Primary: ACR 20 at week 24 Key secondary[c]: not applicable Other[d]: mortality, remission, symptoms, health-related quality of life, AEs

Study reference/ID	**Study type and design**	**Study population**	**Study arms (number of randomised/included patients)**	**Study duration, data cut off(s) and locations**	**Study endpoints**
CLINEVID 2	RCT, double-blind, parallel	Adult patients with active psoriatic arthritis[a] who have had an inadequate response or who have been intolerant to a previous conventional standard therapy of psoriatic arthritis and who may also have been pretreated with TNF inhibitors	A-mab every 4 weeks (N = 128)[e] A-mab every 8 weeks (N = 127) Placebo (N = 126)	▪ Study duration: ▫ Screening: up to 6 weeks ▫ Treatment: 52 weeks (placebo arm: switch to A-mab after 24 weeks) ▫ Follow-up: 8–12 weeks (safety) ▪ Period of study: 8/2017–11/2019 ▪ Data cut-off at week 24[b]: 14 March 2019 ▪ 86 centres in Asia (24), Australia (6), Europe (43), North America (13)	Primary: ACR 20 at week 24 Key secondary[c]: not applicable Other[d]: mortality, remission, symptoms, health-related quality of life, AEs
CLINEVID 4	RCT, double-blind, parallel	Adults with active psoriatic arthritis[f] who have had an inadequate response or who have been intolerant to a previous conventional standard therapy and possibly biologic therapy with TNF inhibitors	B-mab 45 mg (N = 103) B-mab 90 mg (N = 105)[e] Placebo (N = 126)	▪ Study duration: ▫ Screening: up to 6 weeks ▫ Treatment: 52 weeks (placebo arm: switch to B-mab after 24 weeks) ▫ Follow-up: 8 weeks (safety) ▪ Period of study: 2/2010–11/2012 ▪ Data cut-off at week 24[b]: 21 March 2012 ▪ 71 centres in Asia (3), Europe (33), North America (35)	Primary: ACR 20 at week 24 Key secondary[c]: ▪ ACR50 ▪ ACR70 Other[d]: mortality, remission, symptoms, health-related quality of life, AEs

Study reference/ID	**Study type and design**	**Study population**	**Study arms (number of randomised/included patients)**	**Study duration, data cut off(s) and locations**	**Study endpoints**
CLINEVID 5	RCT, double-blind, parallel	Treatment-naive or pretreated[g] adults (≥ 18 years) with plaque psoriasis[h] for at least 6 months before study start, with or without psoriatic arthritis	A-mab (N = 329) Placebo (N = 174)[e] C-mab (N = 334)	▪ Study duration: ▫ Screening: about 4 weeks ▫ Treatment: - blinded treatment phase: until week 48 - open-label extension phase[j]: until week 160 ▫ Observation: until week 160 ▪ Period of study: 12/2014–6/2020 ▪ 101 centres in Asia (24), Australia (7), Europe (32), North America (38)	Primary: PASI 90, IGA score of 0 or 1 Key secondary[c]: not applicable Other[d]: mortality, remission, symptoms, health-related quality of life, AEs
CLINEVID 6	RCT, double-blind, parallel	Treatment-naive or pretreated[g] adults (≥ 18 years) with plaque psoriasis[h] for at least 6 months before study start, with or without psoriatic arthritis	A-mab (N = 496) Placebo (N = 248)[e] C-mab (N = 248)	▪ Study duration: ▫ Screening: about 4 weeks ▫ Treatment: - blinded treatment phase: until week 24 - randomised treatment discontinuation and resumed treatment[i]: week 28 until week 76 - open-label extension phase[j]: until week 160 ▫ Observation: until week 160 ▪ Period of study: 11/2014–7/2020 ▪ 115 centres in Asia (24), Australia (6), Europe (44), North America (41)	Primary: PASI 90, IGA score of 0 or 1 Key secondary[c]: not applicable Other[d]: mortality, remission, symptoms, health-related quality of life, AEs

Study reference/ID	Study type and design	Study population	Study arms (number of randomised/included patients)	Study duration, data cut off(s) and locations	Study endpoints
a: diagnosis according to CASPAR, with ≥ 3 tender and ≥ 3 swollen joints, both at screening and at baseline, and at least one of the following psoriatic arthritis manifestations: distal interphalangeal joint involvement, polyarticular arthritis with absence of rheumatoid nodules, arthritis mutilans, asymmetric peripheral arthritis, or spondylitis with peripheral arthritis; in the CLINEVID 2 study, an additional serum concentration of ≥ 0.3 mg/dL C-reactive protein at screening b: unplanned; data cut-off presented for the benefit assessment to cover the treatment phase until the treatment switch c: only secondary endpoints controlled for multiplicity d: only if included in at least one PICO e: The arm is not relevant for the assessment and is no longer presented in the following tables. f: diagnosis of active psoriatic arthritis at screening defined by ≥ 5 tender and ≥ 5 swollen joints both at screening and at baseline and a serum concentration of ≥ 0.3 mg/dL C-reactive protein at screening (criterion changed from ≥ 0.6 mg/dL after Amendment 3) and at least one of the following psoriatic arthritis manifestations: distal interphalangeal joint involvement, polyarticular arthritis with the absence of rheumatoid nodules, arthritis mutilans, asymmetric peripheral arthritis, or spondylitis with peripheral arthritis g: systemic treatment or phototherapy h: IGA ≥ 3, PASI ≥ 12 and BSA ≥ 10 i: From week 28, patients of all study arms who had not achieved PASI 90 received (continued) treatment with A-mab. Patients in the A-mab arm who had achieved PASI 90 were re-randomised in week 28 to continued treatment with A-mab or treatment discontinuation with resumed A-mab treatment (on 50% loss of the achieved PASI improvement). Patients in the C-mab and placebo arm with PASI 90 response discontinued treatment and received subsequent A-mab treatment on 50% loss of the achieved PASI improvement. Due to lack of comparison, this study phase is not relevant for the assessment and is not shown in the following tables. j: In the open-label extension phase, patients of all study arms were treated with A-mab. Due to lack of comparison, this study phase is not relevant for the assessment and is not shown in the following tables.					
ACR: American College of Rheumatology; AE: adverse event; BSA: body surface area; CASPAR: Classification Criteria for Psoriatic Arthritis; csDMARD: conventional synthetic DMARD; DMARD: disease-modifying antirheumatic drug; n: relevant subpopulation; N: number of randomised patients; PASI: Psoriasis Area and Severity Index; RCT: randomised controlled trial; TNF: tumour necrosis factor					

Table 11: Characterisation of the interventions of included studies

Study reference/ID	Study intervention	Study comparator
CLINEVID 7	D-mab i. v. ▪ 150 mg with infusion duration of 4 hours on day 1 ▪ 450 mg with infusion duration of 1 hour on day 15 and in weeks 24, 48 and 72 + Placebo orally once daily from day 1 to the last day of week 95	E-mab oral ▪ 14 mg once daily from day 1 to the last day of the week 95 + Placebo i. v. on days 1 and 15 and at weeks 24, 48 and 72
	Premedication required ▪ 30 to 60 minutes before infusion: antihistamine (diphenhydramine 50 mg or equivalent, oral) and corticosteroid (dexamethasone 10 to 20 mg or equivalent, oral) **Prohibited pre-treatment medication** ▪ treatment with anti-CD20 or other B cell directed treatment ▪ alemtuzumab, natalizumab, teriflunomide, leflunomide, stem cell transplantation at any time prior to randomisation ▪ ≤ 4 weeks prior to randomisation: phenytoin, warfarin, tolbutamide, St. John's wort or colestyramine ▪ disease-modifying therapies prior to screening: ▫ ≤ 24 months: cladribine ▫ ≤ 6 months: daclizumab, azathioprine, methotrexate or cyclophosphamide ▫ ≤ 90 days: fingolimod or experimental S1P modulators, i. v. immunoglobulin and plasmapheresis ▫ ≤ 30 days: glatiramer acetate, interferons, dimethyl fumarate, laquinimod or glucocorticoids **Permitted concomitant treatment** ▪ antiemetics (preventive or for the treatment of nausea and vomiting) ▪ for the treatment of infusion-related reactions: paracetamol 650 mg, corticosteroids, antihistamines, oxygen, bronchodilators ▪ corticosteroids only in low doses (≤ 10 mg daily prednisone or equivalent) and starting at least 7 days before screening, if not used as premedication or for the treatment of infusion-related reactions ▪ methylprednisolone 1.0 g/day, i. v., for 3-5 days for the treatment of acute relapses[a] **Prohibited concomitant treatment** ▪ other investigational drug treatments ▪ other disease-modifying therapies for MS ▪ radiotherapy, hormonal or immunotherapy for cancer, or other biologic therapy ▪ antihypertensive medication should be withheld 24 hours prior to and throughout the infusion	
CLINEVID 8	same as for CLINEVID 7	

a: New or recurrent neurologic symptoms that evolve gradually over months should be considered disability progression, not an acute relapse and should not be treated with steroids.

CD20: Cluster of Differentiation 20; i. v.: intravenous; MS: multiple sclerosis

Table 13: Information on the course of included studies – planned follow up times

Study reference/ID **Outcome**	**Planned follow-up**
CLINEVID 9	
Overall survival	until death or end of data collection[a]
Symptoms (EORTC QLQ-C30, EORTC QLQ-EN24)	until death or end of data collection[a]
Health status (EQ-5D VAS)	until death or end of data collection[a]
Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-EN24)	until death or end of data collection[a]
AE, severe AE[b], specific AE	until 30 or 42[c] days after the last dose of study medication or until the start of a new antineoplastic therapy (whichever came first)
Serious AE	until 90 days after the last dose of study medication or until the start of a new antineoplastic therapy (whichever came first)
a: up to 4 years after inclusion of the last patient b: according to CTCAE ≥ 3 c: corresponds to the EOT visit; cycle 1 to 6: 30 days after the last dose of study medication, from cycle 7: 42 days after the last dose of study medication	
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organization for Research and Treatment of Cancer; EOT: end of treatment; QLQ-C30: Quality of Life Questionnaire − Core 30; QLQ-EN24: Quality of Life Questionnaire − Endometrial Cancer Module 24; VAS: visual analogue scale	

Table 14: Information on the course of included studies - planned follow up times

Comparison **Study reference/ID** **Outcome**	**Planned follow-up**
F-mab + G-mab+ platinum-based chemotherapy vs. Platinum-based chemotherapy	
CLINEVID 10	
Overall survival	until death or end of study
Symptoms (EORTC QLQ-C30, EORTC QLQ-LC13)	until the 2nd disease progression or death (whichever came first)
Health status (PGIC, EQ-5D VAS)	until the 2nd disease progression or death (whichever came first)
Health-related quality of life (EORTC QLQ-C30)	until the 2nd disease progression or death (whichever came first)
AE	up to 90 days after discontinuation of study medication
PRO-CTCAE	until the 2nd disease progression or death (whichever came first)
H-mab vs. Platinum-based chemotherapy	
CLINEVID 11	
Overall survival	until death or end of study
Symptoms (EORTC QLQ-C30, EORTC QLQ-LC13)	up to 30 days after the last dose of study medication
Health status (EQ-5D VAS)	if treatment ends before progression: until progression or start of a new antineoplastic therapy

Comparison **Study reference/ID** **Outcome**	**Planned follow-up**
Health-related quality of life (EORTC QLQ-C30)	▪ up to 30 days after the last dose of study medication ▪ if treatment ends before progression: until progression or start of a new antineoplastic therapy
AE	up to 30 days after the last dose of study medication
SAE and immune-mediated AE	up to 90 days after the last dose of study medication (or up to 30 days after the last dose of study medication if a new antineoplastic therapy is started; whichever occurred first)
CLINEVID 12	
Overall survival	until death or end of study
Symptoms	not recorded
Health-related quality of life	not recorded
AE	up to 30 days after the last dose of study medication
SAE and immune-mediated AE	up to 90 days after the last dose of study medication (or up to 30 days after the last dose of study medication if a new antineoplastic therapy is started; whichever occurred first)
AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; PGIC: Patient Global Impression of Change; QLQ-C30: Quality of Life Questionnaire – Cancer 30; QLQ-LC13: Quality of Life Questionnaire – Lung Cancer 13; SAE: serious adverse event; VAS: visual analogue scale	

Table 15: Studies included in the assessment of patients with psoriatic arthritis[a] per PICO question

Study reference/ID **Relevant study arms (number of randomised/included patients)**	**Analysed population (number of randomised/included patients)**
PICO 1	
Direct comparison: A-mab vs. C-mab	
CLINEVID 5 A-mab (N = 329) C-mab (N = 334)	Only patients who ▪ had psoritic arthritis in addition to patient-reported symptomatic plaque psoriasis ▪ had been pretreated with at least one csDMARD, but not with bDMARDs (all patients in this subpopulation had received MTX as prior therapy) ▪ had discontinued MTX therapy due to medical reasons Relevant subpopulation: A-mab (n = 25) C-mab (n = 24)

Study reference/ID **Relevant study arms (number of randomised/included patients)**	**Analysed population (number of randomised/included patients)**
CLINEVID 6 A-mab (N = 496) C-mab (N = 248)	Same characteristics as for CLINEVID 5 Relevant subpopulation: A-mab (n = 41) C-mab (n = 21)
CLINEVID 13 A-mab (N = 349) C-mab (N = 330)	Complete study population
a: complete population definition: adult patients with active psoriatic arthritis, who have had an inadequate response to prior DMARD therapy	
bDMARD: biologic DMARD; csDMARD: conventional synthetic DMARD; DMARD: disease modifying antirheumatic drug; MTX: methotrexate; N: number of randomised patients; n: number of patients	

Table 16: Patient baseline characteristics including treatment / study discontinuations for population of patients with dMMR / MSI-H endometrial cancer (Table for direct comparisons)

Study reference/ID **Characteristics** **Category**	**I-mab + carboplatin + paclitaxel** **N = 53[a]**	**Placebo + carboplatin + paclitaxel** **N = 65[a]**
CLINEVID 9		
Age [years], mean (SD)	64 (10)	63 (11)
Ethnicity, n (%)		
Asian	2 (4)	0 (0)
Hawaiian or Pacific Islander	1 (2)	0 (0)
Caucasian	0 (0)	1 (2)
black or African American	4 (8)	6 (9)
unknown	1 (2)	1 (2)
missing	1 (2)	1 (2)
Geographical region, n (%)		
Europe	17 (32)	15 (23)
North America	36 (68)	50 (77)
ECOG-PS, n (%)		
0	28 (54)	39 (60)
1	24 (46)	26 (40)
Histology at last examination, n (%)		
Carcinosarcoma	4 (8)	2 (3)
Endometrioid carcinoma (adenocarcinoma or variants)	45 (85)	54 (83)

Study reference/ID **Characteristics** **Category**	**I-mab + carboplatin + paclitaxel** **N = 53[a]**	**Placebo + carboplatin + paclitaxel** **N = 65[a]**
Mixed carcinoma with ≥ 10 % carcinosarcoma, clear cell or serous histology	1 (2)	4 (6)
other	3 (6)	3 (5)
serous adenocarcinoma	0 (0)	1 (2)
undifferentiated carcinosarcoma	0 (0)	1 (2)
FIGO stage at the start of the study, n (%)		
Stage III	10 (19)	14 (22)
Stage IV	16 (30)	19 (29)
recurrent	27 (51)	32 (49)
Previous radiotherapy of the pelvis, n (%)	19 (36)	22 (34)
Previous surgery for endometrial carcinoma, n (%)	49 (92)	60 (92)
Previous systemic therapy, n (%)	7 (13)	10 (15)
Treatment discontinuation[b], n (%)	29 (56)	56 (86)
Study discontinuation, n (%)	13 (25)	32 (49)
a: relevant subpopulation of the study CLINEVID 9: patients with dMMR / MSI-H endometrial cancer b: Data related to discontinuation of all components. Treatment with carboplatin was not completed as planned in 19 % of patients in the intervention arm and 14 % in the comparator arm. Treatment with paclitaxel was not completed as planned in 17 % of patients in the intervention arm and 23 % in the comparator arm.		
AE: adverse event; dMMR: deficient mismatch repair; ECOG-PS: Eastern Cooperative Oncology Group-Performance Status; FIGO: International Federation of Gynecology and Obstetrics; MSI-H: microsatellite instability-high; N: number of randomised patients; n: number of patients in the category; RCT: randomised controlled trial; RECIST: Response Evaluation Criteria In Solid Tumors; SD: standard deviation		

Table 17: Patient baseline characteristics including treatment / study discontinuations for population of patients with metastatic NSCLC with PD-L1 expression ≥ 50 %[a] (Table for indirect comparisons)

Characteristics **Category**	**F-mab + G-mab + platinum-based chemotherapy vs. Platinum-based chemotherapy**		**H-mab vs. Platinum-based chemotherapy**		**H-mab vs. Platinum-based chemotherapy**	
	CLINEVID 10		**CLINEVID 11**		**CLINEVID 12**	
	F-mab + G-mab + platinum-based chemotherapy	**Platinum-based chemotherapy**	**H-mab**	**Platinum-based chemotherapy**	**H-mab**	**Platinum-based chemotherapy**
	N = 101	**N = 97**	**N = 154**	**N = 151**	**N = 299**	**N = 300**
Age [years], mean (SD)	62 (9)	63 (9)	64 (10)	65 (10)	ND	ND
Sex [f/m], %	27/73	29/71	40/60	37/63	31/69	30/70
Ethnicity, n (%)						
white	55 (54)	44 (45)	125 (81)	126 (83)	ND	ND
Asian	32 (32)	45 (46)	25 (16)	21 (14)	ND	ND
other	14 (14)	8 (8)	2 (1)	0 (0)	ND	ND
unknown	0 (0)	0 (0)	2 (1)	0 (0)	ND	ND
black or African American						
Geographical region, n (%)						
Europe	41 (41)	35 (36)	ND	ND	71 (24)	66 (22)
rest of the world	60 (59)	62 (64)	ND	ND	228 (76)	234 (78
Smoking status, n (%)						
active	19 (19)	17 (18)	34 (22)	31 (21)	57 (19)	59 (20)
former	58 (57)	58 (60)	115 (75)	101 (67)	178 (60)	174 (58)
never	24 (24)	21 (22)	5 (3)	19 (13)	64 (21)	67 (22)
unknown	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
ECOG-PS, n (%)						
0	30 (30)	37 (38)	54 (35)	53 (35)	96 (32)	91 (30)

Characteristics **Category**	**F-mab + G-mab + platinum-based chemotherapy vs. Platinum-based chemotherapy**		**H-mab vs. Platinum-based chemotherapy**		**H-mab vs. Platinum-based chemotherapy**	
	CLINEVID 10		**CLINEVID 11**		**CLINEVID 12**	
	F-mab + G-mab + platinum-based chemotherapy	**Platinum-based chemotherapy**	**H-mab**	**Platinum-based chemotherapy**	**H-mab**	**Platinum-based chemotherapy**
	N = 101	**N = 97**	**N = 154**	**N = 151**	**N = 299**	**N = 300**
1	71 (70)	59 (61)	99 (64)	98 (65)	203 (68)	209 (70)
unknown	0 (0)	1 (1)	1 (< 1)	0 (0)	0 (0)	0 (0)
Histology, n (%)						
squamous	36 (36)	32 (33)	29 (19)	27 (18)	107 (36)	114 (38)
non-squamous	65 (64)	64 (66)	125 (81)	124 (82)	192 (64)	186 (92)
unknown	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Brain metastasis, n (%)	10 (10)	11 (11)	18 (12)	10 (7)	19 (6)	15 (5)
Disease stage, n (%)						
IIIB	0 (0)	0 (0)	1 (< 1)	1 (< 1)	ND	ND
IV	100 (100)	96 (99)	153 (99)	150 (99)	ND	ND
IVA	48 (48)	46 (47)	ND	ND	ND	ND
IVB	53 (52)	50 (52)	ND	ND	ND	ND
unknown	0 (0)	1 (1)	0 (0)	0 (0)	ND	ND
Metastasis staging according to TNM classification, n (%)						
M0	11 (11)	1 (1)	1 (< 1)	1 (< 1)	ND	ND
M1	3 (3)	2 (2)	29 (19)	34 (23)	ND	ND
M1A	36 (36)	35 (36)	47 (31)	41 (27)	ND	ND
M1B	18 (18)	17 (18)	77 (50)	74 (49)	ND	ND
M1C	33 (33)	41 (42)	0 (0)	0 (0)	ND	ND
MX	0 (0)	0 (0)	0 (0)	1 (1)	ND	ND

Characteristics **Category**	**F-mab + G-mab + platinum-based chemotherapy vs. Platinum-based chemotherapy**		**H-mab vs. Platinum-based chemotherapy**		**H-mab vs. Platinum-based chemotherapy**	
	CLINEVID 10		**CLINEVID 11**		**CLINEVID 12**	
	F-mab + G-mab + platinum-based chemotherapy	**Platinum-based chemotherapy**	**H-mab**	**Platinum-based chemotherapy**	**H-mab**	**Platinum-based chemotherapy**
	N = 101	**N = 97**	**N = 154**	**N = 151**	**N = 299**	**N = 300**
unknown	0 (0)	1 (1)	0 (0)	0 (0)	ND	ND
Previous radiotherapy, n (%)	12 (12)	8 (8)	ND	ND	40 (13)	39 (13)
Treatment discontinuation, n (%)	83 (84)	92 (99)	80 (52)	106 (70)	217 (73)	194 (65)
Study discontinuation, n (%)	71 (70)	87 (90)	47 (31)	69 (46)	ND	ND
a: complete population definition: adult patients with metastatic NSCLC with PD-L1 expression ≥ 50 % (without sensitizing EGFR-mutation or ALK-positive mutations, first line therapy)						
ECOG-PS: European Cooperative Oncology Group Performance Status; f: female; m: male; N: number of randomised patients; n: number of patients in the category; ND: no data; PD-L1: Programmed Cell Death-Ligand-1; RCT: randomised controlled trial; SD: standard deviation						

Table 19: Matrix of outcomes in the included RCTs for population of patients with RMS[a] – PICO 1 – direct comparison: D-mab vs. E-mab

Outcomes	**Study reference/ID**	
	CLINEVID 7	CLINEVID 8
All-cause mortality	yes	yes
Annualized relapse rate	yes	yes
Confirmed disability progression (based on EDSS)	yes	yes
Severity of disability (MSFC)	yes	yes
Fatigue (FIS)	yes	no[b]
Health-related quality of life (MSQoL-54)	yes	no[b]
Serious AE	yes	yes
Treatment discontinuation due to AE	yes	yes
Treatment interruption due to AE	no[c]	no[c]
a: complete population definition: adults with RMS, who have not yet received disease-modifying therapy and show no evidence of a severe course of disease b: no data available for the relevant population c: outcome not recorded		
AE: adverse event; EDSS: Expanded Disability Status Scale; FIS: Fatigue Impact Scale; MSFC: Multiple Sclerosis Functional Composite; MSQoL-54: Multiple Sclerosis Quality of Life 54; RMS: relapsing multiple sclerosis		

Table 20: Information on the course of included studies – actual treatment duration and observation periods

Study reference/ID **Outcome category**	**Study intervention**	**Relevant comparator**
CLINEVID 14 **(data cut off: 30.07.2021)**	**J-mab** **N = 301**	**Individualized treatment[a]** **N = 307**
Treatment duration [months]		
Median [Min; Max]	5.0 [0.5; 29.9]	3.4 [0.2; 26.4]
Mean (SD)	6.5 (5.8)	4.5 (4.4)
Observation period [months]		
Overall survival		
Median [Min; Max]	11.7 [0.3; 35.8]	8.5 [0.0; 32.1]
Mean (SD)	13.2 (8.6)	11.1 (8.3)
Symptoms (EORTC QLQ-C30), Health status (EQ-5D VAS), Health-related quality of life (EORTC QLQ-C30)		
Median [Min; Max]	5.4 [0.0; 19.1]	3.5 [0.0; 15.0]
Mean (SD)	5.6 (3.8)	4.1 (3.1)
Adverse events		
Median [Min; Max]	5.6 [1.0; 30.7]	3.8 [1.0; 31.1]
Mean (SD)	7.2 (6.0)	5.3 (5.3)

Study reference/ID **Outcome category**	**Study intervention**	**Relevant comparator**
a: Available chemotherapies were vinflunine, paclitaxel and docetaxel.		
AE: adverse event; EORTC: European Organization for Research and Treatment of Cancer; Max: Maximum; Min: Minimum; N: number of randomised patients; QLQ-C30: Quality of Life Questionnaire − Core 30; SD: standard deviation; VAS: visual analogue scale		

Table 21: Relative effectiveness results (dichotomous outcomes) – direct comparison: K-mab vs. L-mab

Time point **Outcome** **Study reference/ID**	**K-mab**		**L-mab**		**K-mab vs. L-mab**			
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95 %-CI]** **p-value**	**Hypothesis testing**	**RD [95 %-CI]** **p-value**	**Hypothesis testing**
Week 52								
Mortality								
CLINEVID 15[a]	189	5 (2.6)	187	2 (1.1)	2.47 [0.49; 12.59] 0.256	1: NS - 2: NP - 3: NC	0.02 [−0.01; 0.04] 0.256	1: NS - 2: NP - 3: NC
CLINEVID 16[b]	179	3 (1.7)	181	2 (11.0)	1.52 [0.26; 8.97] 0.644	1: NS - 2: NP - 3: NC	0.01 [−0.02; 0.03] 0.644	1: NS - 2: NP - 3: NC
Total[c] (p_H = 0.691; I^2 = 0 %)					2.00 [0.61; 6.58] 0.255	1: NS - 2: NP - 3: NC	0.01 [−0.01; 0.03] 0.245	1: NS - 2: NP - 3: NC
BCVA (improvement by ≥ 10 ETDRS-letters[d])								
CLINEVID 15[a]	189	99 (52.4)	187	107 (57.2)	0.92 [0.76; 1.10] 0.345	1: NS - 2: NP - 3: NC	−0.05 [−0.15; 0.05] 0.345	1: NS - 2: NP - 3: NC
CLINEVID 16[b]	179	110 (61.5)	181	106 (58.6)	1.05 [0.89; 1.24] 0.576	1: NS - 2: NP - 3: NC	0.03 [−0.07; 0.13] 0.576	1: NS - 2: NP - 3: NC
Total[c] (p_H = 0.283; I^2 = 13.3%)					0.98 [0.87; 1.11] 0.771	1: NS - 2: NP - 3: NC	0.01 [−0.08; 0.06] 0.771	1: NS - 2: NP - 3: NC
NEI VFQ-25 (sum score, improvement by ≥ 15 points[e])								
CLINEVID 15[a]	188	46 (24.5)	187	43 (23.0)	1.06 [0.74; 1.53] 0.737	1: NS - 2: NP - 3: NC	0.01 [−0.07; 0.10] 0.737	1: NS - 2: NP - 3: NC
CLINEVID 16[b]	178	37 (20.8)	181	33 (18.2)	1.14 [0.75; 1.74] 0.541	1: NS - 2: NP - 3: NC	0.03 [−0.06; 0.11] 0.541	1: NS - 2: NP - 3: NC
Total[c] (p_H = 0.808; I^2 = 0 %)					1.10 [0.83; 1.44] 0.510	1: NS - 2: NP - 3: NC	0.02 [−0.04; 0.08] 0.510	1: NS - 2: NP - 3: NC

Time point	K-mab		L-mab		K-mab vs. L-mab			
Outcome Study reference/ID	N	Patients with event n (%)	N	Patients with event n (%)	RR [95 %-CI] p-value	Hypothesis testing	RD [95 %-CI] p-value	Hypothesis testing
Reading the "Hypothesis testing" columns: 1: Statistical significance: S = Statistically significant against the alpha level specified in the statistical analysis plan of the corresponding study, NS = Non-significant, NO = Nominal p-value 2: Prespecification: P = Statistical test was prespecified according to the statistical analysis plan of the corresponding study, NP = Not prespecified 3: Multiple hypothesis testing. C = Appropriate control for multiplicity according to the statistical analysis plan and clinical study report of the corresponding study, NC = Not controlled								
a: data cut-off: 11.11.2020 b: data cut-off: 29.06.2020 c: calculated from meta-analysis with Mantel-Haenszel fixed effect model d: Number of patients with an improvement in BCVA by ≥ 10 ETDRS-letters in week 52 compared to baseline on a scale from 0 to 100 points; increasing values correspond to an improvement of symptoms. e: Number of patients with an improvement in NEI VFQ-25 sum score by ≥ 15 points in week 52 compared to baseline on a scale from 0 to 100 points, increasing values correspond to an improvement of health-related quality of life.								
BCVA: Best Corrected Visual Acuity; CI: confidence interval; EDTRS: Early Treatment Diabetic Retinopathy Study; N: number of patients in the analysis; n: number of patients with event; NEI VFQ-25: National Eye Institute Visual Function Questionnaire-25; p_H: p-value from heterogeneity-test based on study*treatment in the meta-analysis; RD: risk difference; RR: relative risk								

Table 23: Relative effectiveness results (continuous outcomes) – direct comparison: M-mab vs. N-mab

Time point	M-mab			N-mab			M-mab vs. N-mab	
Outcome Study reference/ID	N[a]	Values at baseline mean (SD)	Change at month 12 mean (SD)	N[a]	Values at baseline mean (SD)	Change at month 12 mean (SD)	MD [95 %-CI] p-value	Hypothesis testing
Month 12								
Severity of disability (MSFC)								
z-Score[b]								
CLINEVID 17	370	0.03 (0.68)	−0.10 (0.58)	367	0.05 (0.67)	−0.09 (0.57)	−0.01 [−0.06; 0.04] 0.739	1: NS - 2: P - 3: NC

Time point	**M-mab**			**N-mab**			**M-mab vs. N-mab**	
Outcome **Study reference/ID**	**N[a]**	**Values at baseline mean (SD)**	**Change at month 12 mean (SD)**	**N[a]**	**Values at baseline mean (SD)**	**Change at month 12 mean (SD)**	**MD [95 %-CI] p-value**	**Hypothesis testing**
CLINEVID 18	383	0.09 (0.67)	−0.02 (0.59)	360	0.01 (0.69)	−0.06 (0.57)	0.04 [−0.01; 0.09] 0.158	1: NS - 2: P - 3: NC
Total[c] (p_H = 0.25; I^2 = 24 %)							0.02 [−0.02; 0.05] 0.406	1: NS - 2: P - 3: NC
Health-related quality of life (MSQoL-54)								
PHCS[b, d]								
CLINEVID 17	370	69.20 (17,98)	−0.57 (17,50)	367	71,95 (16.41)	−2.39 (17,05)	1.82 [0.21; 3.43] 0.027	1: S - 2: P - 3: NC
CLINEVID 18	380	68.59 (18.47)	−0.05 (20,47)	357	70.11 (18.59)	−1.64 (20,41)	1.59 [−0.10; 3.28] 0.066	1: NS - 2: P - 3: NC
Total[c] (p_H = 0.85; I^2 = 0 %)							1.71 [0.54; 2.88] 0.004	1: S - 2: P - 3: NC
MHCS[b, e]								
CLINEVID 17	370	73.00 (17.68)	−1.76 (21,35)	367	73.38 (17.58)	−2.39 (21,26)	0.64 [−1.37; 2.65] 0.535	1: NS - 2: P - 3: NC
CLINEVID 18	380	71.19 (19.14)	−1.10 (25,54)	360	71.68 (18.64)	−1.58 (25,61)	0.47 [−1.65; 2.59] 0.662	1: NS - 2: P - 3: NC
Total[c] (p_H = 0.85; I^2 = 0 %)							0.56 [−0.90; 2.02] 0.452	1: NS - 2: P - 3: NC

Reading the "Hypothesis testing" columns:
1. Statistical significance: S = Statistically significant against the alpha level specified in the statistical analysis plan of the corresponding study, NS = Non-significant, NO = Nominal p-value
2. Prespecification: P = Statistical test was prespecified according to the statistical analysis plan of the corresponding study, NP = Not prespecified
3. Multiple hypothesis testing. C = Appropriate control for multiplicity according to the statistical analysis plan and clinical study report of the corresponding study, NC = Not controlled

Time point	**M-mab**			**N-mab**			**M-mab vs. N-mab**	
Outcome **Study reference/ID**	**N[a]**	**Values at baseline mean (SD)**	**Change at month 12 mean (SD)**	**N[a]**	**Values at baseline mean (SD)**	**Change at month 12 mean (SD)**	**MD [95 %-CI] p-value**	**Hypothesis testing**
a: relevant subpopulation of CLINEVID 17 and CLINEVID 18: treatment-naïve patients with RRMS or previously treated patients whose disease is not highly active b: Higher (increasing) values mean better symptoms; positive effects (intervention minus control) mean an advantage for M-mab. c: calculated from meta-analysis. Heterogeneity was tested using the Cochran Q test. d. The following subscales are summarised in this score: physical function, role limitations-physical, pain, energy, health perceptions, social function, health distress and sexual function e. The following subscales are summarised in this score: role limitations-emotional, emotional well-being, cognitive function, health distress, overall quality of life								
CI: confidence interval; MD: mean difference; MHCS: Mental Health Composite Score; MSFC: Multiple Sclerosis Functional Composite; N: number of patients in the analysis; p_H: p-value from test for heterogeneity; PHCS: Physical Health Composite Score; RRMS: Relapsing-remitting multiple sclerosis; SD: standard deviation								

Table 24: Safety outcomes (dichotomous outcomes) – direct comparison: D-mab vs. E-mab

Time point	**D-mab**		**E-mab**	
Outcome **Study reference/ID**	**N**	**Patients with event n (%)**	**N**	**Patients with event n (%)**
Week 96				
At least one AE				
CLINEVID 7	273	235 (86.1)	275	245 (89.1)
CLINEVID 8	272	251 (92.3)	273	256 (93.8)
Serious AE				
CLINEVID 7	273	31 (11.4)	275	19 (6.9)
CLINEVID 8	272	28 (10.3)	273	21 (7.7)
Severe AE [CTCAE grade]				
CLINEVID 7				
Grade ≥ 3	273	72 (26.4)	275	43 (15.6)
Grade 3[a]	273	60 (22.0)	275	39 (14.2)
Grade 4[a]	273	8 (2.9)	275	3 (1.1)
Grade 5[a]	273	4 (0.7)	275	1 (0.4)
CLINEVID 8				
Grade ≥ 3	272	44 (16.2)	273	34 (12.5)
Grade 3[a]	272	35 (12.9)	273	30 (11.0)
Grade 4[a]	272	7 (2.6)	273	2 (0.7)
Grade 5[a]	272	2 (0.7)	273	2 (0.7)
Death related to AE				
CLINEVID 7	273	1 (0.4)	275	0 (0.0)
CLINEVID 8	272	0 (0.0)	273	0 (0.0)
Treatment discontinuation due to AE				
CLINEVID 7	273	18 (6.6)	275	2 (0.7)
CLINEVID 8	272	5 (1.8)	273	2 (0.7)
Treatment interruption due to AE				
CLINEVID 7	273	10 (3.7)	275	3 (1.1)
CLINEVID 8	272	8 (2.9)	273	2 (0.7)
Infusion-related reaction[b]				
CLINEVID 7	273	119 (43.6)	275	31 (11.3)
CLINEVID 8	272	144 (52.9)	273	41 (15.0)
Infections and infestations[b]				
CLINEVID 7	273	15 (5.5)	275	6 (2.2)
CLINEVID 8	272	12 (4.4)	273	10 (3.7)
a: Considers the worst grade of severity of the patients. b: As requested by member state(s) in their PICOs.				
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; N: number of patients in the analysis; n: number of patients with event; PICO: Population – Intervention – Comparator – Outcome				

Table 28: Subgroup analyses (continuous outcomes) – direct comparison: K-mab vs. L-mab

Time point **Outcome** **Variable** **Study reference/ID** **Subgroups**	**K-mab**			**L-mab**			**K-mab vs. L-mab**	
	N	**Values at baseline mean (SD)**	**Values at week 52 mean (SD)**	**N**	**Values at baseline mean (SD)**	**Values at week 52 mean (SD)**	**MD [95 %-CI] p-value**	**Hypothesis testing**
Week 52								
BCVA – study eye								
Age								
CLINEVID 15								
< 65 years of age	104	65.48 (10.41)	79.22 (9.95)	93	65.83 (12.85)	77.35 (11.91)	0.99[a] [−1.19; 3.17] 0.371	1: NS - 2: P - 3: NC
≥ 65 years of age	85	67.99 (8.53)	75.12 (9.24)	94	64.52 (11.94)	74.53 (9.41)	−3.63[a] [−5.94; −1.32] 0.002	1: S - 2: P - 3: NC
Per study							Interaction[b]: 0.022	
CLINEVID 16								
< 65 years of age	100	67.07 (10.11)	79.66 (10.51)	102	64.42 (10.50)	75.56 (11.68)	1.73[a] [−0.55; 4.02] 0.137	1: NS - 2: P - 3: NC
≥ 65 years of age	79	64.66 (11.47)	75.09 (10.74)	79	62.78 (13.10)	71.54 (11.93)	1.68[a] [−0.87; 4.22] 0.196	1: NS - 2: P - 3: NC
Per study							Interaction[b]: 0.331	
Total[c] (p_H = 0.014; I^2 = 73 %)							Interaction[b]: 0.022	
< 65 years of age	204	66.26 (10.27)	79.43 (10.19)	195	65.09 (11.67)	76.45 (11.80)	1.34[c] [−0.23; 2.90] 0.095	1: NS - 2: P - 3: NC
≥ 65 years of age	164	66.38 (10.16)	75.10 (9.98)	173	63.73 (12.48)	73.14 (10.72)	−1.14[c] [−2.85; 0.57] 0.190	1: NS - 2: P - 3: NC

Time point	**K-mab**			**L-mab**			**K-mab vs. L-mab**	
Outcome **Variable** **Study reference/ID** **Subgroups**	**N**	**Values at baseline mean (SD)**	**Values at week 52 mean (SD)**	**N**	**Values at baseline mean (SD)**	**Values at week 52 mean (SD)**	**MD [95 %-CI] p-value**	**Hypothesis testing**
Reading the "Hypothesis testing" columns: 1. Statistical significance: S = Statistically significant against the alpha level specified in the statistical analysis plan of the corresponding study, NS = Non-significant, NO = Nominal p-value 2. Prespecification: P = Statistical test was prespecified according to the statistical analysis plan of the corresponding study, NP = Not prespecified 3. Multiple hypothesis testing. C = Appropriate control for multiplicity according to the statistical analysis plan and clinical study report of the corresponding study, NC = Not controlled								
a: MD obtained from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + baseline category + age + treatment * age + visit * age + treatment * age * visit b: Likelihood-ratio test for the comparison of the model from footnote a against the model based on treatment + visit + treatment * visit + baseline category + age + visit * age c: calculated from meta-analysis. MD obtained from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + baseline category + study + treatment * study + age + treatment * age + visit * age + treatment * age * visit								
BCVA: Best Corrected Visual Acuity; CI: confidence interval; MD: mean difference; MMRM: Mixed-Effect Model Repeated Measure; N: number of patients in the analysis; p_H: p-value from test for heterogeneity based on study*treatment in the meta-analysis; SD: standard deviation								

Table 29: Matrix of outcomes in the included studies for population of patients with metastatic NSCLC with PD-L1 expression ≥ 50 %[a] – PICO 1 – indirect comparison: F-mab + G-mab + platinum-based chemotherapy vs. H-mab

Outcomes	**Comparison Study reference/ID**			**Indirect comparison methods**
	F-mab + G-mab + platinum-based chemotherapy vs. Platinum-based chemotherapy	**H-mab vs. Platinum-based chemotherapy**		
	CLINEVID 10	CLINEVID 11	CLINEVID 12	
Overall survival	yes	yes	yes	Bucher
Symptoms (EORTC QLQ-C30 and EORTC QLQ-LC13)	no[b]	yes	no[c]	no[d]
Health status (EQ-5D VAS)	no[b]	yes	no[c]	no[d]
Health status (PGIC)	no[b]	no[b]	no[c]	no[d]
Health-related quality of life (EORTC QLQ-C30)	no	yes	no[c]	no[d]
Serious AE	yes	yes	no[e]	no[d]
Severe AE (CTCAE ≥ 3)	no[b]	yes	no[e]	no[d]
Treatment discontinuation due to AE	yes	yes	no[e]	no[d]
PRO-CTCAE	yes	no[c]	no[c]	no[d]
Immune-mediated AE	yes	yes	no[e]	no[d]

a: complete population definition: adult patients with metastatic NSCLC with PD-L1 expression ≥ 50 % (without sensitizing EGFR-mutation or ALK-positive mutations, first line therapy)
b: data not suitable
c: outcome not recorded
d: indirect comparison not suitable; see running text for reasons
e: no information for the relevant subpopulation

AE: adverse event; ALK: anaplastic lymphoma kinase; CTCAE: Common Terminology Criteria for Adverse Events; EGFR: epidermal growth factor receptor; EORTC: European Organisation for Research and Treatment of Cancer; NSCLC: Non-small-cell lung cancer; PD-L1: Programmed Death-Ligand-1; PGIC: Patient Global Impression of Change; PRO-CTCAE: Patient-reported Outcome – CTCAE; QLQ-C30: Quality of Life Questionnaire – Cancer 30; QLQ-LC13: Quality of Life Questionnaire – Lung Cancer 13; VAS: visual analogue scale

Table 30: Information on the course of included studies – actual treatment duration and observation periods

Comparison **Study reference / ID** **Outcome category**	**Study intervention**	**Relevant comparator**
F-mab + G-mab + platinum-based chemotherapy vs. Platinum-based chemotherapy		

Comparison **Study reference / ID** **Outcome category**	**Study intervention**	**Relevant comparator**
CLINEVID 10 **(data cut off: 12.03.2021)**	**F-mab + G-mab + platinum-based chemotherapy** **N = 338 / n[a] = 99**	**Platinum-based chemotherapy** **N = 337 / n[a] = 93**
Treatment duration [months]		
Total		
Median [Min; Max]	7.4 [0.2; 43.7]	4.1 [0.2; 34.5]
Mean (SD)	13.7 (12.5)	5.5 (5.8)
F-mab		
Median [Min; Max]	4.6 [0.2; 8.3]	
Mean (SD)	4.3 (1.5)	
G-mab		
Median [Min; Max]	7.4 [0.2; 43.7]	
Mean (SD)	13.6 (12.5)	
Platinum-based chemotherapy		
Median [Min; Max]	3.7 [0.2; 43.7]	4.1 [0.2; 34.5]
Mean (SD)	9.1 (11.1)	5.5 (5.8)
Observation period [months]		
Overall Survival		
Median [Min; Max]	15.9 [0.3; 55.8]	10.6 [0; 55.8]
Mean (SD)	18.9 (13.4)	12.1 (10.0)
Symptoms (EORTC QLQ-C30, EORTC QLQ-LC13), Health status (EQ-5D VAS)		
Median [Min; Max]	8.4 [0.1; 42.9]	4.7 [0; 33.4]
Mean (SD)	9.9 (6.2)	5.6 (3.9)
Health status (PGIC)[b]		
Median [Min; Max]	9.0 [0.7; 42.9]	5.9 [0.7; 33.4]
Mean (SD)	10.2 (5.8)	6.3 (3.2)
Health-related quality of life (EORTC QLQ-C30)		
Median [Min; Max]	8.4 [0.1; 42.9]	4.7 [0; 33.4]
Mean (SD)	9.9 (6.2)	5.6 (3.9)
Adverse events[c]		
Median [Min; Max]	9.0 [0.3; 55.6]	5.7 [0.2; 46.6]
Mean (SD)	10.2 (6.3)	6.0 (4.1)
H-mab vs. Platinum-based chemotherapy		
CLINEVID 11 **(data cut-off 09.05.2016)**	**H-mab** **N = 154**	**Platinum-based chemotherapy** **N = 150**
Treatment duration [months]		
Median [Min; Max]	7.0 [0.0; 18.7]	3.5 [0.0; 16.8]

Comparison **Study reference / ID** **Outcome category**	**Study intervention**	**Relevant comparator**
Mean (SD)	6.8 (4.8)	4.0 (3.5)
Observation period [months]	NI	NI
CLINEVID 12 **(data cut-off 26.02.2018)**	**H-mab** **N = 637 / n[a] = 299**	**Platinum-based chemotherapy** **N = 637 / n[a] = 300**
Treatment duration [months]	NI	NI
Observation period [months]	NI	NI
a: relevant subpopulation: adult patients with metastatic NSCLC with PD-L1 expression ≥ 50 % b: Data refer to 96 patients (intervention arm) vs. 80 patients (comparator arm). c: The observation period was calculated as the time from the first dose of study medication to the earliest time of occurrence of the following: 90 days after the last dose of study medication; date of start of first follow-up therapy or date of death.		
EORTC: European Organisation for Research and Treatment of Cancer; Max: Maximum; Min: Minimum; N: number of randomised patients; NI: no information; NSCLC: Non-small-cell lung cancer; PD-L1: Programmed Death-Ligand-1; PGIC: Patient Global Impression of Change; QLQ-C30: Quality of Life Questionnaire - Cancer 30; QLQ-LC13: Quality of Life Questionnaire - Lung Cancer 13; SD: standard deviation; VAS: visual analogue scale		

Table 40: Adverse events (all) by SOC and PT including effect estimates

Time point **Study reference/ID** **Safety outcome** **SOC[a]** **PT[a]**	**K-mab** **N= 189[b]** **Patients with event n (%)**	**L-mab** **N = 187[b]** **Patients with event n (%)**	**K-mab vs. L-mab** **RR [95 %-CI]; p-value**	**K-mab vs. L-mab** **RD [95 %-CI]; p-value**
Week 52				
CLINEVID 15[c]				
Total AE	155 (82.0)	148 (79.1)	1.04 [0.94; 1.14]; 0.483	0.03 [−0.05; 0.11]; 0.482
Blood and lymphatic system disorders	9 (4.8)	10 (5.3)	0.89 [0.37; 2.14]; 0.796	−0.01 [−0.05; 0.04]; 0.795
Cardiac disorders	12 (6.3)	14 (7.5)	0.85 [0.40; 1.78]; 0.664	−0.01 [−0.06; 0.04]; 0.664
Eye disorders	91 (48.0)	82 (79.1)	1.10 [0.88; 1.37]; 0.404	0.04 [−0.06; 0.14]; 0.403
Conjunctival haemorrhage	17 (9.0)	21 (11.2)	0.80 [0.44; 1.47]; 0.473	−0.02 [−0.08; 0.04]; 0.472
Diabetic retinal oedema	10 (5.3)	11 (5.9)	0.90 [0.39; 2.07]; 0.803	−0.01 [−0.05; 0.04]; 0.803
Cataract	12 (6.3)	12 (6.4)	0.99 [0.46; 2.15]; 0.979	−0.00 [−0.05; 0.05]; 0.979
Vitreous floaters	11 (5.8)	6 (3.2)	1.81 [0.68; 4.80]; 0.231	0.03 [−0.02; 0.07]; 0.221
Vitreous detachment	11 (5.8)	5 (2.7)	2.18 [0.77; 6.14]; 0.142	0.03 [−0.01; 0.07]; 0.129
Gastrointestinal disorders	27 (14.3)	19 (10.2)	1.41 [0.81; 2.44]; 0.225	0.04 [−0.02; 0.11]; 0.221
General disorders and administration site conditions	16 (8.5)	14 (7.5)	1.13 [0.57; 2.25]; 0.726	0.01 [−0.04; 0.06]; 0.726
Infections and infestations	68 (36.0)	50 (26.7)	1.35 [0.99; 1.82]; 0.056	0.09 [−0.00; 0.19]; 0.052
Nasopharyngitis	16 (8.5)	13 (7.0)	1.22 [0.60; 2.46]; 0.583	0.02 [−0.04; 0.07]; 0.582
Urinary tract infection	15 (7.9)	7 (3.7)	2.12 [0.88; 5.08]; 0.092	0.04 [−0.01; 0.09]; 0.081
Investigations	20 (10.6)	19 (10.2)	1.04 [0.57; 1.89]; 0.893	0.00 [−0.06; 0.07]; 0.893
Injury, poisoning and procedural complications	15 (7.9)	24 (12.8)	0.62 [0.34; 1.14]; 0.124	−0.05 [−0.11; 0.01]; 0.119
Metabolism and nutrition disorders	35 (18.5)	18 (9.6)	1.92 [1.13; 3.27]; 0.016	0.09 [0.02; 0.16]; 0.012

Time point **Study reference/ID** **Safety outcome** **SOC[a]** **PT[a]**	**K-mab** **N= 189[b]** **Patients with event n (%)**	**L-mab** **N = 187[b]** **Patients with event n (%)**	**K-mab vs. L-mab** **RR [95 %-CI]; p-value**	**K-mab vs. L-mab** **RD [95 %-CI]; p-value**
Musculoskeletal and connective tissue disorders	19 (10.1)	12 (6.4)	1.57 [0.78; 3.14]; 0.205	0.04 [−0.02; 0.09]; 0.199
Nervous system disorders	17 (9.0)	19 (10.2)	0.89 [0.48; 1.65]; 0.701	−0.01 [−0.07; 0.05]; 0.701
Renal and urinary disorders	14 (7.4)	17 (9.1)	0.81 [0.41; 1.60]; 0.554	−0.02 [−0.07; 0.04]; 0.553
Vascular disorders	24 (12.7)	22 (11.8)	1.08 [0.63; 1.86]; 0.782	0.01 [−0.06; 0.08]; 0.782
Hypertension	17 (9.0)	16 (8.6)	1.05 [0.55; 2.02]; 0.881	0.00 [−0.05; 0.06]; 0.881
Respiratory, thoracic and mediastinal disorders	22 (11.6)	18 (9.6)	1.21 [0.67; 2.18]; 0.527	0.02 [−0.04; 0.08]; 0.526
Skin and subcutaneous tissue disorders	13 (6.9)	9 (3.7)	1.84 [0.75; 4.50]; 0.183	0.03 [−0.01; 0.08]; 0.174
a: events that occurred in at least one study arm in ≥ 10 patients b: SAF c: data cut-off: 11.11.2020				
AE: adverse event; CI: confidence interval; N: number of patients in the analysis; n: number of patients with event; PT: Preferred Term; RD: risk difference; RR: relative risk; SAF: safety set; SOC: System Organ Class				

Table 44: Study design and methodology for studies CLINEVID 7 and CLINEVID 8[a]

CONSORT Item[b]	**Characteristic**	**Study information**
-	Study objective	
2 b	Precise objectives, problem and hypotheses	The main objective of the CLINEVID 7 and CLINEVID 8 studies was to evaluate the annualised relapse rate as well as the safety and tolerability of D-mab compared to E-mab in patients with RMS.
-	Methods	
3	Study design	
3a	Description of the study design (e.g. parallel, factorial) including allocation ratio	Randomised, multicentre, double-blind, active-controlled, double-dummy study. Eligible patients were randomised 1:1 into the treatment arms (D-mab or E-mab).
3b	Relevant changes in the methodology after the study has started (e.g. inclusion/ exclusion criteria, with justification)	The original protocols of the CLINEVID 7 and CLINEVID 8 studies (version 1.0) were finalised on 14 April 2017. The participants were

CONSORT Item[b]	Characteristic	Study information
		included in the study from protocol version 2.1. **Relevant changes after version 2.1** Version 3.0 (dated 03 August 2017): ▪ sections 7.2.1.3 and 7.2.1.4 have been updated to reflect the changes to the AEs in the Investigator's Brochure. Version 3.1 (dated 20 October 2017): ▪ use of version 4.03 of the National Cancer Institute grading system for UE. ▪ functional system (FS) scale scores should correspond to the participant's symptoms. ▪ for relapses, participants were only required to re-consent if the relapse was confirmed. ▪ malignancy was included as a reason for discontinuation. ▪ the treating neurologist performed the MSFC and SDMT examinations. ▪ the BART (Blinded Assessment Relapse Team) was asked to reassess the sample size when 210 of 220 patients per arm had been randomised. ▪ the EDSS scores determined by the investigating neurologist were not to be shared with the treating neurologist and the principal investigator if the latter was also the treating neurologist. ▪ AEs, including pregnancies and medically confirmed deaths, were recorded from the day the informed consent form was signed until 20 weeks after discontinuation. ▪ the events of special interest defined in the protocol (section 9.10.6) were updated. Version 4.0 (dated 17 January 2020): ▪ clarification of the exclusion criteria to avoid possible misinterpretation. Deletion of criterion number 18 and revision of criteria 5; 14 and 23. Version 5.0 (dated 04 September 2020): ▪ update of secondary endpoints. ▪ update of tertiary endpoints. ▪ clarification/correction of exclusion criteria 13b; 15 and 21. ▪ definition of relapses that were medically confirmed by the treating neurologist.

CONSORT Item[b]	Characteristic	Study information
		▪ added requirement that participants had to re-consent if the treating neurologist medically confirmed a relapse. ▪ update of the reference time point for participants who re-consented to participate in the study after a confirmed relapse. ▪ clarification of the definition of disability progression. ▪ clarification that the evaluation of disability was a post-hoc analysis. ▪ clarification on the follow-up of AEs when a participant discontinued the study. ▪ clarification that participant-reported outcomes (FIS, MSQoL) should also be collected at the early treatment discontinuation visit. ▪ definition of IRR and clarification that these should be collected separately. ▪ updated definitions of the ITT, mITT and PP populations. ▪ further definition of TEAE. ▪ clarification that hospitalisations due to the underlying disease (MS disease progression) and due to a relapse did not have to be reported as SAEs. ▪ protocol list for the AESI was replaced with a reference to the valid investigator brochure.
4	Test subjects / patients	
4a	Inclusion/exclusion criteria for test subjects/patients	**Inclusion criteria** ▪ age: 18 to 55 years. ▪ diagnosis of RMS. ▪ ≥ 2 relapses in the previous two years or 1 relapse in the year prior to screening and/or ≥ 1 Gd-enhancing lesion. ▪ abnormalities in the brain suggestive of MS; detected by MRI. ▪ active disease. ▪ EDSS 0 to 5.5 (inclusive) at the time of screening. ▪ B-cell count ≥ 5 % of total lymphocytes. ▪ neurologically stable for ≥ 30 days prior to screening and at baseline. ▪ participants who were not of childbearing age, who had undergone surgical sterilisation and participants of childbearing age whose serum pregnancy test was negative at the start of the study. Participants of childbearing potential and all

CONSORT Item[b]	Characteristic	Study information
		male partners were required to have agreed to use a medically/clinically acceptable method of contraception throughout the treatment period and for 20 weeks after the end of active treatment. Participants of childbearing potential must have agreed to undergo a urine pregnancy test every four weeks during active treatment and during the follow-up period. ▪ fertile male study participants who were sexually active with women of childbearing age had to have agreed to use a condom during the treatment period and for a further 20 weeks after the end of active treatment. Consent to an accelerated withdrawal procedure following the last dose of study medication or early withdrawal from the study. ▪ willingness and ability to comply with the study procedures and follow-up procedures. Written informed consent was given. **Exclusion criteria** ▪ treatment with anti-CD20 therapy or another treatment directed against B cells. ▪ treated with one of the following therapies at any time prior to randomisation: ▫ alemtuzumab; ▫ natalizumab; ▫ teriflunomide; ▫ leflunomide; ▫ stem cell transplantation. ▪ E-mab contraindicated or intolerance to the use of E-mab. ▪ therapies that were not permitted (at least four weeks prior to randomisation): Phenytoin, warfarin, tolbutamide, St John's wort or colestyramine. ▪ treated with disease-modifying therapies in the months prior to screening: ▫ within 24 months with cladribine; ▫ within 6 months with daclizumab, azathioprine, methotrexate or cyclophosphamide. ▫ within 90 days with fingolimod or with experimental S1P modulators, IV immunoglobulin and plasmapheresis.

CONSORT Item[b]	Characteristic	Study information
		▫ within 30 days with glatiramer acetate, interferons, dimethyl fumarate, laquinimod or glucocorticoids. ▪ diagnosis of primary progressive MS (PPMS). ▪ pregnant or breastfeeding women. ▪ duration of disease ≥ 10 years since onset in patients with an EDSS score ≤ 2.0. ▪ MRI and/or gadolinium contraindicated. ▪ known presence of other neurological diseases that could be mistaken for MS. ▪ current signs or known history of clinically significant infection. These included: ▫ chronic or ongoing active viral, bacterial, or fungal infection that required long-term systemic treatment; for example, but not limited to: progressive multifocal leukoencephalopathy (PML), chronic renal infection, chronic chest infection with bronchiectasis, tuberculosis (TB), or active hepatitis C; ▫ previous severe opportunistic or atypical infections; ▫ history of positive serology for hepatitis B or hepatitis C or human immunodeficiency virus (HIV). ▪ history of clinically significant trauma to the central nervous system (CNS) (e.g. traumatic brain injury, brain contusion, spinal cord compression). ▪ history of liver disease, including but not limited to: ▫ known history of active hepatitis B or C at any time prior to randomisation. Or known history of active hepatitis A within three years prior to randomisation; ▫ presence of clinically significant chronic liver or biliary disease; ▫ moderate or severe liver dysfunction; defined as Child-Pugh score B or C, respectively, based on measurement of total bilirubin, serum albumin, INR (International Normalised Ratio) and presence/absence and severity of ascites and hepatic encephalopathy; ▫ one of the following abnormal laboratory values at screening or first infusion: - ALT/SGPT > 2 × ULN (upper limit of normal);

CONSORT Item[b]	Characteristic	Study information
		- AST/SGOT > 2 × ULN (upper limit of normal). ▪ previous diagnosis of congenital or acquired immunodeficiency (AIDS). ▪ history of renal dysfunction, including but not limited to: ▫ hypoproteinaemia (e.g. severe renal disease or nephrotic syndrome) with serum albumin < 3.0 g/dl. ▫ severe renal insufficiency requiring renal dialysis. ▪ medically significant adverse events (including allergic reactions), either current or history, due to: ▫ corticosteroids; ▫ diphenhydramine; ▫ murine or murine/human chimeric antibodies. ▪ participants with significantly impaired bone marrow function or with significant anaemia, leucopenia or thrombocytopenia. ▫ haematocrit < 24 % and/or ▫ absolute white blood cell count < 4,000 cells/mm^3 and/or ▫ platelet count < 150,000 cells/mm^3 and/or ▫ absolute neutrophil count ≤ 1,500 cells/mm^3. ▪ absolute lymphocyte count lower than 1,000/microlitre. ▪ any severe and/or uncontrolled medical illness or other condition that could have interfered with participation in the study; such as: ▫ symptomatic or history of confirmed congestive heart failure (New York Heart Association functional class III - IV). ▫ QTcF in women > 450 ms; in men > 30 ms. ▫ angina pectoris that is not well controlled by medication. ▫ poorly controlled or clinically significant atherosclerotic vascular disease, including cerebrovascular event, transient ischaemic attack, angioplasty, cardiac or vascular stenting in the six months prior to screening. ▪ other significant concurrent, uncontrolled medical conditions, including but not limited to cardiac, renal, hepatic, haematological, gastrointestinal, endocrine,

CONSORT Item[b]	Characteristic	Study information
		immunodeficiency, pulmonary, cerebral, psychiatric or neurological conditions that could have interfered with the participant's safety, reliable participation in the study, evaluation of endpoints, or required the use of medications that were not permitted by the protocol (as determined by the principal investigator). ▪ participation in another clinical intervention study. Participation in a non-interventional study was subject to sponsor approval. ▪ lack of ability or willingness to comply with study procedures or follow-up procedures described in the protocol. ▪ lack of immunity to varicella as determined by screening for IgG antibodies to varicella-zoster virus. The participant could be vaccinated and rescreened. ▪ vaccination with a live virus within two months prior to randomisation. ▪ history or presence of malignancy (except for surgically removed basal cell carcinoma or squamous cell carcinoma of the skin), lymphoproliferative disease or history of complete radiotherapy to the lymph nodes or bone marrow transplantation.
4b	Study organization and location where the study is conducted	CLINEVID 7 The study was conducted at 60 study centres in nine countries in Europe and North America. CLINEVID 8 The study was conducted at 50 study centres in eight countries in Europe and North America.
5	Interventions Precise information on the planned interventions in each group and on the administration, etc.	**Intervention arm** D-mab ▪ strength and pharmaceutical form: 15 ml (10 mg/ml) or 6 ml (25 mg/ml) in a glass vial for single use, diluted with sodium chloride (NaCl) 0.9 % to a total volume of 250 ml. ▪ dosage: 150 mg in week 1 on day 1 with an infusion duration of four hours, followed by 450 mg in week 3 on day 15 and in weeks 24; 48 and 72 with an infusion duration of one hour each. ▪ route of administration: IV infusion. Placebo ▪ pharmaceutical dosage form: tablet.

CONSORT Item[b]	Characteristic	Study information
		▪ dosage: One tablet daily starting in week 1 on day 1 until the last day of week 95. ▪ route of administration: oral. **Comparator arm** <u>Placebo</u> ▪ pharmaceutical dosage form: 15 ml or 6 ml in a glass vial for single use, diluted with NaCl 0.9 % to a total volume of 250 ml. ▪ dosage: Administration in week 1 on day 1 with an infusion duration of four hours, followed by an infusion in week 3 on day 15 and in weeks 24; 48 and 72 with an infusion duration of one hour each. ▪ route of administration: IV infusion. <u>E-mab</u> ▪ strength and pharmaceutical dosage form: 14 mg tablet. ▪ dosage: One tablet daily, starting in week 1 on day 1 until the last day of week 95. ▪ route of administration: oral. **Duration of treatment** The maximum study duration for each participant was 120 weeks and comprised a four-week screening phase, a 96-week treatment phase and a 20-week follow-up phase.
6	Target criteria	
6a	Clearly defined primary and secondary target criteria, survey times, possibly all survey methods used to optimize the quality of results (e.g. multiple observations, training of the examiners) and possibly information regarding the validation of survey instruments	**Primary endpoint (efficacy)** The primary efficacy endpoint was the annualised relapse rate (ARR), defined as the number of relapses per participant-year confirmed by the Independent Relapse Adjudication Panel (IRAP). The ARR estimate for a treatment group was calculated by dividing the total number of relapses experienced by participants in that treatment group by the total treatment duration of participants in that specific treatment group. Participants were treated for up to 96 weeks. **Secondary endpoints (efficacy)** ▪ total number of Gd-enhancing T1 lesions at week 96, determined by MRI. ▪ total number of new and enlarging T2 hyperintense lesions at week 96 as determined by MRI.

CONSORT Item[b]	Characteristic	Study information
		▪ time to 12-week confirmed disability progression (12W-CDP) during the 96-week double-blind treatment period.* ▪ proportion of participants with No Evidence of Disease Activity (NEDA) status from week 24 to 96. ▪ proportion of participants with worsening SDMT from baseline to week 96. ▪ percentage change in brain volume from baseline to week 96. *CDP over at least 12 weeks during the 96-week treatment period was analysed using pooled data from CLINEVID 7 and CLINEVID 8. **Tertiary endpoints (efficacy)** ▪ change in MSFC score from baseline to week 96. ▪ time to 24W-CDP. ▪ time to 12W CDI. ▪ time to 24W CDI. ▪ results on health status (MSQoL-54 including SF-36, FIS, hospitalisation, administration of steroids, inability to work). ▪ total volume of Gd-enhancing T1 lesions over the course of the treatment period as determined by MRI. ▪ volume of T2 lesions. ▪ volume of T1 hypointense lesions (black holes). ▪ proportion of participants without disability progression at weeks 24; 48 and 96. ▪ proportion of participants with relapses. ▪ time to first confirmed relapse. **Pharmacokinetics** ▪ serum concentration of D-mab. **Safety** ▪ physical examination. ▪ vital signs. ▪ ECG (electrocardiogram). ▪ laboratory values for safety. ▪ AE. **Other variables** ▪ immunogenicity; presence of ADA (anti-drug antibodies) against D-mab.

CONSORT Item[b]	Characteristic	Study information
		▪ pharmacokinetic parameters (proportion of $CD19^+$ B cells).
6b	Changes in the target criteria after the study has started, with justification	**Change in the endpoint hierarchy (secondary and tertiary)** Tertiary to secondary ▪ percentage of participants for whom SDMT worsened from baseline to week 96. Secondary to tertiary ▪ volume of T2 lesions. ▪ volume of T1 hypointense lesions (black holes). ▪ percentage of participants without disability progression at weeks 24; 48 and 96.
7	Case number	
7a	How were the case numbers determined?	The starting point for determining the sample size was the 40 per cent reduction in ARR with O-mab in the CLINEVID 19 and 20 studies. The ARR assumption for E-mab was based on the results of the CLINEVID 21 and CLINEVID 22 studies (ARR in CLINEVID 22 0.319). For the calculation, a shift to lower rates was assumed as a conservative estimate (ARR assumption for E-mab: 29%). An ARR reduction of 40 % with D-mab compared to E-mab resulted in an ARR with D-mab of 0.174. Under these assumptions, 200 patients per group were required. A two-sided test of the null hypothesis H_O: RR = 1.00 against the alternative H_a: RR ≠ 1.00 was applied using maximum likelihood estimation in a negative binomial regression. A sample size of 220 patients in each group with an average exposure time of 1.75 years resulted in a power of 80 % to determine a rate ratio of 0.60 (corresponding to a 40 % reduction) with a type I error (alpha) of 0.05 overall and a negative binomial regression distribution of relapses over 100 weeks. To allow for possible losses of up to 10 %, the required sample size was increased to 220 per group or 440 in total.
7b	If necessary, description of interim analyses and criteria for premature discontinuation of the study	No interim efficacy analyses were planned for these studies. An interim analysis to re-evaluate the sample size by a blinded assessment relapse team (BART) after randomisation of 210 of the 220 participants was planned.

CONSORT Item[b]	Characteristic	Study information
		The Data Safety Monitoring Board (DSMB) was able to discontinue the study for safety reasons after reviewing the safety data.
8	Randomization, generation of treatment sequence	
8a	Method for generating random allocation	The investigator had access to an IWRS to enrol the patients. Here he also received unique identification numbers and the numbers of the study drug kits.
8b	Details (e.g. block randomization, stratification)	The individuals were assigned dynamically to the treatment arms. No stratification factors were used.
9	Randomization, allocation concealment, execution of allocation (e.g. numbered containers; central randomization by fax/ phone), information if concealment was ensured until allocation	Eligible patients were randomised 1:1 to the following treatment arms: D-mab or E-mab. Randomisation/assignment to treatment of eligible patients was performed using IWRS (Medidata Balance), which was integrated into the EDC system (Electronic Data Capture; Medidata Rave). The IWRS assigned patients to the treatment to be administered by dynamic randomisation. The randomisation of the drug kits for the study was created as a kit list.
10	Randomization, execution Who conducted the allocation, who entered the test subjects/patients in the study and who allocated the test subjects/patients to the groups?	During screening, patients were registered in the electronic data capture (EDC) system. The system automatically assigned them a patient identification number. Once an individual qualified, the study site accessed the EDC randomisation form to confirm that the patient would be randomised. The trial site's action in the EDC triggered the randomisation process in the IWRS (Interactive Web Response System) to assign patients to one of the two treatments. The IWRS was therefore the back-end engine that processed transactions from the front-end EDC system through which the user interacted at the study centre.
11	Blinding	
11a	Were the a) test subjects/patients and/or b) those who conducted the intervention/ treatment, and/or c) those who assessed the target variables blinded or not blinded, how was blinding performed?	All persons involved in the conduct and analysis of the study, including investigators, study centre staff and the sponsor, were blinded to treatment until database closure and until the study was officially unblinded. Unblinding of a participant's treatment was permitted if deemed necessary by the investigator and clinical monitor for immediate medical care. The relapse assessment by the IRAP was communicated to the treating neurologist,

CONSORT Item[b]	Characteristic	Study information
		who then notified the participant and updated the eCRF accordingly. The IRAP was not involved in the subsequent treatment decisions of the participants. To maintain independence and blinding, the investigating neurologist did not receive the report. In addition, neither the treating neurologist nor the participant could communicate the IRAP decision to the investigating neurologist. The treating neurologist counselled the participant after receiving the IRAP decision as described in the protocol.
11b	If relevant, description of the similarity of interventions	Double-dummy study; to ensure adequate blinding, all oral study drugs were prepared as identical tablets and in identical containers, and all intravenous study drugs were prepared in identical vials.
12	Statistical methods	
12a	Statistical methods for assessing the primary and secondary target criteria	**Analysis populations** Safety population All participants who received at least one dose of study drug (D-mab or E-mab with corresponding placebo). All safety analyses, including toxicity and anti-drug antibodies, were performed in the safety population according to the actual treatment received. Intention-to-treat population (ITT) All randomised participants. Sensitivity analyses of the main endpoints are based on the ITT population. Modified intention-to-treat population (mITT) All participants in the ITT population who received at least one dose of study drug and for whom at least one efficacy assessment was available at baseline and post-baseline. The primary efficacy analyses (for primary, secondary and tertiary efficacy endpoints, except those related to MRI) were based on the mITT population. Per-protocol population (PP) All participants in the mITT group who were treated for at least 1.75 years and for whom no significant protocol deviation occurred that would have affected the efficacy analysis. The PP population was only used for sensitivity analyses of the primary endpoint and the main secondary endpoints. mITT-MRI population

CONSORT Item[b]	Characteristic	Study information
		Participants in the mITT population for whom MRI efficacy assessments were available at baseline and post-baseline. PP-MRI population All participants in the PP population for whom MRI efficacy assessments were available at baseline and post-baseline. PK population All participants in the safety population who had at least one PK sample taken at baseline and post-baseline. **Analyses of effectiveness** Primary analysis The primary analysis was conducted using mITT with negative binomial regression. The response variable in the model was the total number of confirmed relapses that occurred between the time of randomisation and the day of the last treatment. Covariates were treatment group, EDSS strata (EDSS score at baseline ≤ 3.5 versus > 3.5) and region of clinic. There were two treatment groups: E-mab or D-mab. The log-transformed standardised treatment duration was included in the model as an "offset variable" to account for the difference in treatment duration between patients. The standardised treatment duration was defined as follows: (time of last treatment - randomisation time + 1) / 365.25. For the comparison of D-mab with E-mab, two-sided 95% CIs of the rate ratio were given. The estimated relapse rate of each treatment group and the difference between the two were reported together with the corresponding two-sided 95% CIs. The primary efficacy endpoint was tested with a two-sided type I error of 5%. If the null hypothesis for the primary efficacy endpoint was rejected, the null hypothesis for the secondary efficacy endpoints was tested. Secondary endpoints The key secondary endpoints were tested using a hierarchical gatekeeping approach. The order was predetermined. Each test maintained a type I error of 0.05. *MRI* The number of Gd-enhancing T1 lesions and the number of new and enlarging T2

CONSORT Item[b]	Characteristic	Study information
		hyperintense lesions were assessed for treatment effects using negative binomial regression. The offset variable was the log-transformed number of MRI scans after baseline, and covariates were region, baseline EDSS strata, and baseline lesion number. The analysis of the percent change in brain volume since baseline was performed using MMRM analysis. The models included fixed effects of treatment, region, EDSS strata at baseline, visit (nominal visits in three stages with week 24; week 96 and week 96), the time-dependent treatment effect (treatment-by-visit interaction) and the baseline brain volume (cube root transformed). An unstructured correlation matrix was used. The parameters were estimated using restricted maximum likelihood with the Newton-Raphson method. The degrees of freedom in the denominator were estimated using the Satterthwaite approximation. *NEDA* The proportion of people who were free of measurable disease activity (NEDA) was calculated at week 96. NEDA status was defined as no evidence of disease activity, i.e. no IRAP-confirmed relapses, no MRI activity (no Gd-enhancing T1 lesions and no new/enlarging T2 lesions), and no disability progression confirmed after 12 weeks. Any evidence of disease activity between weeks 24 and 96 was considered failure to achieve NEDA status. Any evidence of disease activity prior to week 24 was disregarded. In case of early discontinuation at any time (including prior to week 24), even if no event was reported prior to early discontinuation, the patient was considered not to have achieved NEDA status. The NEDA proportion was analyzed using logistic regression. Adjustments to baseline values were made analogously to the analysis of the primary endpoint, without offsetting the treatment duration, but with log-transformed lesion counts from the MRI at baseline (non-enhancing T1 lesions; T2 lesions; Gd-enhancing lesions). To avoid zero values in the log transformation of the MRI values, 1 was added to each observation before transformation. *SDMT* The SDMT total score was defined as the total number of correct answers. A deterioration in

CONSORT Item[b]	Characteristic	Study information
		the SDMT was defined as a decrease of at least four points on any SDMT assessment after baseline through week 96. The proportion of patients with a deterioration in the SDMT was compared using logistic regression. Adjustments to baseline values were made analogously to the analysis of the primary endpoint, without offsetting the treatment duration, but with log-transformed lesion counts from the MRI at baseline (non-enhancing T1 lesions; T2 lesions; Gd-enhancing lesions). To avoid zero values in the log transformation of the MRI values, 1 was added to each observation before transformation. *EDSS/Disability* The 12W-CDP was defined as an increase in EDSS of at least one point (EDSS at baseline ≤ 5.5) or at least 0.5 points (EDSS at baseline > 5.5). Disability progression was considered confirmed if the increase in EDSS score was confirmed at a regularly scheduled visit twelve weeks after the first documentation of neurological deterioration (unscheduled visits were not considered). The time to occurrence of a 12W-CDP was the time to the EDSS change defined above. For each of these events, the time from randomization to the time of the first measurement of the EDSS increase was the "time to event". If no event occurred, it was censored at the time of the last scheduled EDSS assessment. The 12W-CDP summary tables showed the proportion of patients with 12W-CDP through week 96 with the corresponding 95% CIs for each treatment group. The median time to event with two-sided 95% CIs and the proportion of patients without an event at each time point were estimated using Kaplan-Meier methods. The EDSS results were summarized as continuous and categorical variables by the planned assessment time point and treatment group. All data collected to assess the EDSS were listed. <u>Tertiary endpoints</u>

CONSORT Item[b]	Characteristic	Study information
		All tertiary analyses were assessed with a type I error of 0.05 and without multiplicity adjustment. *MSFC* Change in MSFC was tested using linear mixed models that included all planned assessment points. Covariates were the baseline score together with covariates from the primary endpoint analysis. *Other disability endpoints* The analysis of time to 24W-CDP, to 12W-CDI and to 24W-CDI was performed using the same approach as the 12W-CDP assessment. *Fatigue Impact Scale (FIS)* Change in FIS was tested using a linear mixed model that included all planned assessment points. Covariates were the baseline score together with covariates from the primary endpoint analysis. *MSQoL-54* Change in MSQoL-54 was tested using linear mixed models that included all planned assessment points. Covariates were the baseline score plus covariates from the primary endpoint analysis. *Work absence* The percentage of work hours missed was compared between treatment arms using Wilcoxon rank sum tests. *Steroid use* The number of IRAP-confirmed flares treated with steroids was analysed in the same way as the primary endpoint. *Analysis of other variables* The proportion of patients hospitalized for a suspected MS relapse and the proportion of patients who received steroids to treat an IRAP-confirmed relapse were analysed in the same way as NEDA status. Variables related to lesion volume (total volume of Gd-enhancing T1 lesions, volume of T2 lesions, volume of T1 hypointense lesions [black holes]) were analysed using MMRM. Time to first confirmed relapse was defined as: time of relapse onset – time of randomization +1. Censoring was performed at the end of treatment. The analysis was performed as for the analysis of time to CDP.

CONSORT Item[b]	Characteristic	Study information
		The proportions of patients with relapse and patients without disability progression at different time points were estimated using the Kaplan-Meier method. **Safety analyses** The safety analyses were based on the incidence, intensity and type of AEs and clinically significant changes in participants' physical examination, vital signs and clinical laboratory values. The safety analyses were performed in the safety population. Safety variables were tabulated and presented by actual treatment administered. Exposure to study treatment and reasons for discontinuation of study treatment were also tabulated. Immunogenicity (ADA) results were listed for the safety population. **Pharmacokinetic analyses** Serum D-mab concentrations were tabulated. All PK analyses were performed using the PK population. **Pharmacodynamic analyses** B lymphocyte ($CD19^+$ B cell) counts were tabulated for each planned time point along with absolute and percent changes from baseline. **Statistical Analysis Plan** Statistical analyses were performed according to the Statistical Analysis Plan (SAP) version 3.0 with the following changes: ▪ The definition of a TEAE was revised to remove the cut-off of onset or worsening 30 days after the last dose. The definition included any AEs that occurred on or after the first dose of study drug, as well as AEs that occurred before the first dose of study drug and that increased in severity on or after the first dose of study drug. ▪ Two subgroups with small sample sizes were regrouped. For analysis of the subgroup by race, the categories “White” or “Other race” were used. The number of relapses in the two years prior to study entry was reported as “≤ 1”, “2” and “≥ 3”.

CONSORT Item[b]	**Characteristic**	**Study information**
12b	Additional analyses, such as subgroup analyses and adjusted analyses	Subgroup analyses for the primary efficacy variable were performed by: ▪ gender (male; female) ▪ racial origin (white; other) ▪ age category (< 38; ≥ 38). Age of 38 was assumed to be close to the median age of all randomised patients ▪ region (US and Western Europe: US; Spain, UK; Eastern Europe: all other countries) ▪ EDSS strata at baseline (≤ 3;5, > 3.5) ▪ number of relapses in the previous two years (≤ 1; 2; and ≥ 3) ▪ treatment with approved disease-modifying MS drugs prior to study entry (yes; no) ▪ number of Gd-enhancing lesions at baseline (0; ≥ 1)
-	Results	
13	Patient flow (including flow chart for illustration after the table)	See flow chart
13a	Number of study participants for each of the treatment groups formed through randomization, who a) were randomised, b) actually received the planned treatment/intervention, c) were considered in the analysis of the primary target criterion	<u>CLINEVID 7</u> a) D-mab: 274 patients; E-mab: 275 patients b) D-mab: 273 patients; E-mab: 275 patients c) D-mab: 271 patients; E-mab: 274 patients <u>CLINEVID 8</u> a) D-mab: 272 patients; E-mab: 273 patients b) D-mab: 272 patients; E-mab: 273 patients c) D-mab: 272 patients; E-mab: 272 patients
13b	For each group: Description of lost and excluded patients after randomization including justification	<u>CLINEVID 7</u> In the D-mab arm, 34 patients discontinued the study. The reasons were as follows: ▪ adverse events: 17 ▪ consent withdrawn: 6 ▪ investigator's decision: 4 ▪ pregnancy: 2 ▪ lost to follow-up: 2 ▪ lack of efficacy: 2 ▪ alternative treatment: 1 In the E-mab arm, 23 patients discontinued the study. The reasons were as follows: ▪ consent withdrawn: 15 ▪ investigator's decision: 2 ▪ lost to follow-up: 2 ▪ lack of efficacy: 2 ▪ Adverse events: 1

CONSORT Item[b]	**Characteristic**	**Study information**
		▪ other: 1 CLINEVID 8 In the D-mab arm, 18 patients discontinued the study; the reasons were as follows: ▪ adverse events: 3 ▪ consent withdrawn: 6 ▪ investigator decision: 2 ▪ pregnancy: 4 ▪ COVID-19: 3 In the E-mab arm, 34 patients discontinued the study; the reasons were as follows: ▪ consent withdrawn: 23 ▪ investigator decision: 2 ▪ lost to follow-up: 2 ▪ lack of efficacy: 2 ▪ alternative treatment: 2 ▪ adverse events: 1 ▪ pregnancy: 1 ▪ other: 1
14	Inclusion / recruitment	
14a	More details on the time period the test subjects/patients started the study and on follow-up monitoring	CLINEVID 7 Start of study (first participant; first visit): September 19, 2017. Completion of study (last participant; last visit): November 6, 2020. CLINEVID 8 Start of study (first participant; first visit): August 25, 2017. Completion of study (last participant; last visit): November 12, 2020.
14b	Information why the study ended or was terminated	The studies were completed as planned.
a. The design and methodology of the studies CLINEVID 7 and CLINEVID 8 are identical. The information is therefore provided in one table. b: according to CONSORT 2010		

List of references

1. Mueller C. Efficacy of A-mab Compared With C-mab and Placebo for Psoriasis in Specific Body Regions: A Secondary Analysis of 2 Randomized Clinical Trials. J Clin Evidence 2018; 154(6): 676-683. https://doi.org/10.1001/jce.2018.0793.

2. Mueller J. Improvement in Patient-Reported Outcomes (Dermatology Life Quality Index and the Psoriasis Symptoms and Signs Diary) with A-mab in Moderate-to-Severe Plaque Psoriasis: Results from the Phase III CLINEVID 5 and CLINEVID 6 Studies. J Clin Evidence 2019; 20(1): 155-164. https://doi.org/10.1007/s40257-018-0396-z1.

3. Mueller H. Maintenance of clinical response and consistent safety profile with up to 3 years of continuous treatment with A-mab: Results from the CLINEVID 5 and CLINEVID 6 trials. J Clin Evidence 2020; 82(4): 936-945. https://doi.org/10.1016/j.jce.2019.11.040.

4. Mueller I. Safety of A-mab in patients with moderate-to-severe psoriasis treated through 100 weeks: a pooled analysis from the randomized CLINEVID 5 and CLINEVID 6 studies. J Clin Evidence 2019; 180(5): 1039-1049. https://doi.org/10.1111/jce.17454.

5. Mueller G. Efficacy and safety of A-mab, an anti-interleukin-23 monoclonal antibody, compared with C-mab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: Results from the phase III, double-blind, placebo- and active comparator-controlled CLINEVID 6 trial. J Clin Evidence 2017; 76(3): 418-431. https://doi.org/10.1016/j.jce.2016.11.042.

6. Mueller B. Efficacy and safety of A-mab in patients with active psoriatic arthritis who are inadequate responders to tumour necrosis factor inhibitors: results through one year of a phase IIIb, randomised, controlled study (CLINEVID 1). J Clin Evidence 2022; 81(3): 359-369. https://doi.org/10.1136/jce-2021-220991.

7. Mueller A. A-mab in patients with active psoriatic arthritis who were biologic-naive or had previously received TNFalpha inhibitor treatment (CLINEVID 2): a double-blind, randomised, placebo-controlled phase 3 trial. J Clin Evidence 2020; 395(10230): 1115-1125. https://doi.org/10.1016/S0140-6736(20)30265-81.

8. Mueller F. B-mab Treatment and Improvement of Physical Function and Health-Related Quality of Life in Patients With Psoriatic Arthritis. J Clin Evidence 2016; 68(12): 1812-1822. https://doi.org/10.1002/jce.23000.

9. Mueller E. B-mab, an anti-IL-12/23 p40 monoclonal antibody, inhibits radiographic progression in patients with active psoriatic arthritis: results of an integrated analysis of radiographic data from the phase 3, multicentre, randomised, double-blind, placebo-controlled CLINEVID 23 and CLINEVID 4 trials. J Clin Evidence 2014; 73(6): 1000-1006. https://doi.org/10.1136/jce-2013-204741.

10. Mueller D. Efficacy and safety of B-mab in psoriatic arthritis patients with peripheral arthritis and physician-reported spondylitis: post-hoc analyses from two phase III, multicentre, double-blind, placebo-controlled studies (CLINEVID 23/CLINEVID 4). J Clin Evidence 2016; 75(11): 1984-1988. https://doi.org/10.1136/jce-2015-209068.

11. HTD A. A Study of A-mab in the Treatment of Participants With Moderate to Severe Plaque-Type Psoriasis (CLINEVID 5) [online]. 2014 [Accessed: 18.09.2024]. URL: https://ClinicalTrials.gov/show/NCT02207213.

12. HTD A. A Phase 3, Multicenter, Randomized, Double-blind, Placebo and Active Comparator-controlled Study Evaluating the Efficacy and Safety of A-mab for the Treatment of Subjects with Moderate to Severe Plaque-type Psoriasis with Randomized Withdrawal and Retreatment [online]. 2014 [Accessed: 18.09.2024]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2014-000719-51.

13. HTD A. A Study of A-mab in the Treatment of Participants With Moderate to Severe Plaque-Type Psoriasis With Randomized Withdrawal and Retreatment (CLINEVID 6) [online]. 2014 [Accessed: 18.09.2024]. URL: https://ClinicalTrials.gov/show/NCT02207442.

14. HTD A. Phase 3, Multicenter, Randomized, Double-blind, Placebo and Active Comparator controlled Study Evaluating the Efficacy and Safety of A-mab for the Treatment of Subjects with Moderate to Severe Plaque-type Psoriasis with Randomized Withdrawal and Retreatment [online]. 2015 [Accessed: 18.09.2024]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2014-000720-81.

15. HTD A. Study of A-mab in Participants With Active Psoriatic Arthritis and an Inadequate Response to Anti-Tumor Necrosis Factor Alpha (Anti-TNF Alpha) Therapy (CLINEVID 1) [online]. 2019 [Accessed: 18.09.2024]. URL: https://ClinicalTrials.gov/show/NCT03796885.

16. HTD A. Phase 3b, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of A-mab Administered Subcutaneously in Participants with Active Psoriatic Arthritis and an Inadequate Response to Anti-Tumor Necrosis Factor Alpha (Anti-TNFα) Therapy [online]. 2019 [Accessed: 18.09.2024]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2018-003214-14.

17. HTD A. A Study Evaluating the Efficacy and Safety of A-mab Administered Subcutaneously in Participants With Active Psoriatic Arthritis Including Those Previously Treated With Biologic Anti -Tumor Necrosis Factor (TNF) Alpha Agent(s) (CLINEVID 2) [online]. 2017 [Accessed: 18.09.2024]. URL: https://ClinicalTrials.gov/show/NCT03162769.

18. HTD A. A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study Evaluating the Efficacy and Safety of A-mab Administered Subcutaneously in Subjects with Active Psoriatic Arthritis including those Previously Treated with Biologic Anti-TNFα Agent(s) [online]. 2017 [Accessed: 18.09.2024]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-001163-73.

19. HTD A. A Study of the Safety and Efficacy of B-mab in Patients With Psoriatic Arthritis With and Without Prior Exposure to Anti-TNF Agents [online]. 2010 [Accessed: 18.09.2024]. URL: https://ClinicalTrials.gov/show/NCT01077326.

20. HTD A. A Phase 3 Multicenter, Randomized, Double-blind, Placebo-controlled trial of B-mab, a Fully Human anti-IL-12/23p40 Monoclonal Antibody, Administered Subcutaneously, in Subjects with Active Psoriatic Arthritis Including Those Previously Treated With Biologic Anti-TNFα Agent(s) [online]. 2010 [Accessed: 18.09.2024]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2009-012265-06.

21. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. A-mab (Psoriasis-Arthritis) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2021 [Accessed: 18.09.2024]. URL: https://www.iqwig.de/download/a20-211_A-mab_nutzenbewertung-35a-sgb-v_v1-0.pdf.

22. Canadian Agency for Drugs and Technologies in Health. CADTH Reimbursement Review A-mab (Psorya) [online]. 2022 [Accessed: 18.09.2024]. URL: https://www.cda-amc.ca/sites/default/files/DRR/2022/SR0733%20Psorya%20PsA%20-%20Draft%20CADTH%20Recommendation%20for%20Posting%20October%2020%2C%202022.pdf.

23. HTD A. JA0010EN3005 (CLINEVID 5) Clinical Study Report [unpublished].

24. HTD A. JA0010EN3006 (CLINEVID 6) Clinical Study Report [unpublished].

25. HTD A. JA0010EN3001 (CLINEVID 1) Clinical Study Report [unpublished].

26. HTD A. JA0010EN3002 (CLINEVID 2) Clinical Study Report [unpublished].

27. HTD A. JA0010EN3004 (CLINEVID 4) Clinical Study Report [unpublished].