Drugs (2021) 81:1349–1353
https://doi.org/10.1007/s40265-021-01561-7

ADISINSIGHT REPORT

Amivantamab: First Approval

Yahiya Y. Syed[1]

Published online: 22 July 2021

Abstract
Amivantamab (amivantamab-vmjw; Rybrevant™), a bispecific monoclonal antibody targeting epidermal growth factor receptor (EGFR) and mesenchymal epithelial transition factor (MET), is being developed by Janssen Biotech for the treatment of non-small cell lung cancer (NSCLC). On 21 May 2021, amivantamab received its first approval in the USA for the treatment of adult patients with locally advanced or metastatic NSCLC harbouring EGFR Exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy. Amivantamab is in preregistration for NSCLC in the EU, Australia, Japan, Canada, Switzerland and China. This article summarizes the milestones in the development of amivantamab leading to this first approval for NSCLC.

Digital Features for this AdisInsight Report can be found at https://doi.org/10.6084/m9.figshare.14818641.

Amivantamab (Rybrevant™): Key points

A bispecific EGFR and MET antibody being developed by Janssen Biotech for the treatment of NSCLC.

Received its first approval on 21 May 2021 in the USA.

Approved for use in adult patients with locally advanced or metastatic NSCLC harbouring EGFR Exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy.

1 Introduction

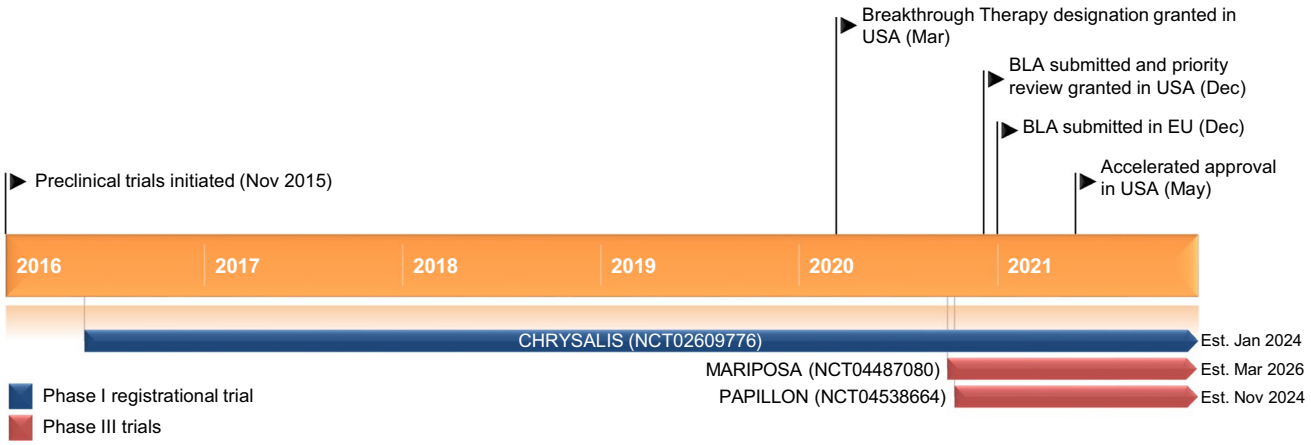
Amivantamab (amivantamab-vmjw; Rybrevant™) is a fully human bispecific monoclonal antibody directed against epidermal growth factor receptor (EGFR) and mesenchymal epithelial transition factor (MET) [1]. It is being developed by Janssen Biotech, using Genmab's DuoBody® technology, for the treatment of non-small cell lung cancer (NSCLC). Activating EGFR mutations acquire resistance to EGFR tyrosine kinase inhibitors (TKIs) through multiple mechanisms, including secondary EGFR mutation and activation of the c-MET pathway [2, 3]. Amivantamab concurrently binds to the extracellular domains of both EGFR and MET, thereby blocks their interactions with the cognate ligands, resulting in the disruption of these signalling pathways [2, 3].

Intravenous amivantamab received its first approval on 21 May 2021 in the USA for the treatment of adult patients with locally advanced or metastatic NSCLC harbouring EGFR Exon 20 insertion (Ex20ins) mutations, as detected by a US FDA-approved test (Sect. 2.6), whose disease has progressed on or after platinum-based chemotherapy [4, 5]. This was an accelerated approval based on the overall response rate (ORR) and duration of response (DOR) seen in the phase I CHRYSALIS study. Continued approval for this indication may be contingent upon verification and description of clinical benefits in confirmatory trials. The recommended dosage of amivantamab is 1050 mg and 1400 mg in patients weighing < 80 kg and ≥ 80 kg, respectively, weekly for every 4 weeks, then every 2 weeks until disease progression or

This profile has been extracted and modified from the *AdisInsight* database. *AdisInsight* tracks drug development worldwide through the entire development process, from discovery, through preclinical and clinical studies to market launch and beyond.

✉ Yahiya Y. Syed
dru@adis.com

[1] Springer Nature, Private Bag 65901, Mairangi Bay, Auckland 0754, New Zealand



Key milestones in the development of amivantamab for the treatment of non-small cell lung cancer. *BLA* Biologics License Application

unacceptable toxicity. The first dose should be split into two and administered on days 1 and 2 [4].

Amivantamab has been filed for approval for the treatment of NSCLC in the EU, Australia, Japan, Canada, Switzerland and China, under the US FDA's Project Orbis. The agent is also undergoing phase III development for NSCLC worldwide. In addition to the intravenous formulation, Janssen Biotech is developing a human hyaluronidase-based subcutaneous formulation of amivantamab, using Halozyme Therapeutics' ENHANZE™ technology; this formulation is under phase I development in the UK, the USA and South Korea.

1.1 Company Agreements

In July 2020, Guardant Health signed an agreement with Janssen Biotech to pursue regulatory approval and commercialisation of Guardant360® CDx as a companion diagnostic for amivantamab in the treatment of NSCLC in Europe, USA, Canada and Japan [6].

In December 2014, Halozyme Therapeutics entered into a global collaboration and license agreement with Janssen Biotec to develop and commercialize subcutaneous therapeutics, combining Janssen's proprietary compounds with Halozyme's ENHANZE™ technology [7]. ENHANZE is based on a proprietary recombinant human hyaluronidase enzyme that temporarily modifies hyaluronan to facilitate dispersion and absorption of injected drugs. In December 2019, Janssen elected EGFR and MET targets on an exclusive basis as part of amivantamab development [8].

In July 2012, Genmab entered into a research and development collaboration with Janssen Biotech for up to 10 bispecific antibody programmes targeting multiple diseases, using Genmab's DuoBody® technology [9]. The agreement was expanded in December 2013 to include up to 10 additional programmes [10]. Genmab is entitled to upfront, milestone and royalty payments [9, 10].

2 Scientific Summary

2.1 Pharmacodynamics

Amivantamab was produced from engineered Chinese hamster ovary cell lines with low levels of fucosylation, resulting in enhanced binding to FcγRIIIa on immune cells and enhanced antibody-dependent cell-mediated cytotoxicity (ADCC) [2, 3]. Amivantamab exhibits multiple mechanism of action, including Fc-independent (blockade of EGFR and MET signalling via ligand binding and receptor inactivation) and Fc-mediated (ADCC) mechanisms, with the latter being essential for maximal tumour inhibition [2, 3]. Interaction of the amivantamab Fc domain with Fcγ receptors on natural killer cells leads to ADCC and with Fcγ receptors on monocytes and macrophages leads to cytokine production and trogocytosis [11]. Trogocytosis, which downmodulates EGFR and MET receptors and their downstream signalling, is considered a dominant mechanism of action of amivantamab [11].

In Ba/F3 and/or patient-derived cells harbouring various EGFR Ex20ins mutations, treatment with amivantamab led to EGFR and MET internalization, inhibition of EGFR- and MET-mediated downstream signalling cascades, induction of ADCC and apoptosis, and subsequent inhibition of tumour cell proliferation [12]. Consistent with these findings, amivantamab decreased tumour volume in a patient-derived xenograft mice model harbouring an EGFR Ex20ins mutation [12]. Amivantamab also exhibited potent antitumor

activity in patient-derived cell and xenograft models of acquired resistance to first-, second- and third-generation TKIs [13].

2.2 Pharmacokinetics

Following intravenous administration, amivantamab exposure increased proportionally over a dose range of 350–1750 mg [4]. Steady state was achieved by the ninth infusion, with an accumulation ratio of 2.4. The mean volume of distribution of amivantamab is 5.13 L, mean clearance is 360 mL/day and the terminal half-life is 11.3 days [4].

2.3 Therapeutic Trials

The efficacy of amivantamab in patients with locally advanced or metastatic NSCLC and EGFR Ex20ins mutations was demonstrated in an open-label, multicentre, multicohort, phase I trial (CHRYSALIS; NCT02609776) [4, 14]. Eligible patients had progressed on or after platinum-based chemotherapy [4]. Patients with untreated brain metastases and those with a history of interstitial lung disease (ILD) requiring prolonged treatment with steroids or other immunosuppressive agents were among those excluded. Patients received the recommended phase II dose of amivantamab 1050 mg (if bodyweight was < 80 kg) or 1400 mg (if bodyweight was ≥ 80 kg) once weekly for 4 weeks, then every 2 weeks until disease progression or unacceptable toxicity. The ORR (based on the RECIST v1.1 criteria) was the main efficacy endpoint and the DOR was an additional endpoint, both evaluated by a blinded independent central review. In the efficacy population ($n = 81$), the median age was 62 years, 59% of patients were female, 49% were Asian, 37% were White, 2.5% were Black, 67% had Eastern Cooperative Oncology Group performance status of 1, 95% had adenocarcinoma and 46% had received prior immunotherapy. All patients had metastatic disease, with 22% having previously treated brain metastases. Patients had received a median two prior therapies. The ORR was 40% (95% CI 29–51%) [complete response 3.7%, partial response 36%]. The median DOR was 11.1 months (95% CI 6.9 to not estimable); 63% of patients had a DOR of ≥ 6 months [4]. Median progression-free and overall survival were 8.3 and 22.8 months, respectively [14].

Features and properties of amivantamab

Alternative names	Ami-LC-MD; Amivantamab admixed with rHuPH20; Amivantamab-vmjw; Bispecific EGFR-cMet antibody; CNTO4424; EGFR-MET bispecific antibody; EGFRxcMET bispecific antibody; JNJ 372; JNJ-61186372; JNJ-6372; RYBREVANT
Class	Antineoplastics; bispecific antibodies; immunotherapies
Mechanism of action	Dual blockade of EGFR and MET signalling; antibody-dependent cell cytotoxicity (ADCC)
Route of administration	Intravenous; subcutaneous
Pharmacodynamics	Induces EGFR and MET internalization; inhibits EGFR- and MET-mediated downstream signalling; induces ADCC and apoptosis; inhibits tumour cell proliferation
Pharmacokinetics	Dose proportional exposure; mean volume of distribution 5.13 L; mean clearance 360 mL/day; terminal half-life 11.3 days; volume of distribution and clearance increased with increasing bodyweight
Most frequent adverse events	Rash, infusion-related reactions, paronychia, musculoskeletal pain, dyspnoea, nausea, fatigue, oedema, stomatitis, cough, constipation, and vomiting
ATC codes	
WHO ATC code	L01 (Antineoplastic Agents)
EphMRA ATC code	L1 (Antineoplastics)
CAS number (Unique Ingredient Identifier)	2171511-58-1 (0JSR7Z0NB6)

Amivantamab volume of distribution and clearance increased with increasing bodyweight [4]. At the same dose, exposures were 30–40% lower in patients weighing ≥ 80 kg than in those weighing < 80 kg. A 1400 mg dose in patients weighing ≥ 80 kg and a 1050 mg dose in those weighing < 80 kg produced a similar level of exposure. Age (32–87 years), sex, creatinine clearance (CL_{CR}; 29–276 mL/min) or mild hepatic impairment [total bilirubin ≤ upper limit of the normal (ULN) and AST > ULN or total bilirubin ≤ 1.5 × ULN] had no clinically relevant effect on the pharmacokinetics of amivantamab. The effect of severe kidney function impairment (CL_{CR}15–29 mL/min) or moderate (total bilirubin 1.5–3 × ULN) to severe (total bilirubin > 3 × ULN) hepatic impairment has not been evaluated [4].

Key clinical trials of amivantamab (Janssen Biotech)

Drug(s)	Indication	Phase	Status	Location(s)	Identifier
Amivantamab, lazertinib, osimertinib	NSCLC	III	Recruiting	Multinational	MARIPOSA, NCT04487080, EudraCT2020-000743-31, CR108856, 73841937NSC3003
Amivantamab, carboplatin, pemetrexed	NSCLC	III	Recruiting	Multinational	PAPILLON, NCT04538664, EudraCT2020-000633-40, CR108850, 61186372NSC3001
Amivantamab, lazertinib, carboplatin, pemetrexed	NSCLC	I	Recruiting	Multinational	CHRYSALIS, NCT02609776, EudraCT2018-003908-38, JapicCTI184169, CR108064, 61186372EDI1001
Amivantamab, carboplatin, lazertinib, pemetrexed	NSCLC	I	Recruiting	Multinational	CHRYSALIS-2, NCT04077463, EudraCT2020-000747-31, CR108656, 73841937NSC1001
Amivantamab (SC), hyaluronidase	Solid tumours	I	Recruiting	Multinational	NCT04606381, EudraCT2020-003225-36, CR108891, 61186372NSC1003
Amivantamab	NSCLC	EAP	Recruiting	USA	NCT04599712, CR108905, 61186372LUC4001

EAP expanded access programme, *NSCLC* non-small cell lung cancer (metastatic or advanced disease)

In part 1 of CHRYSALIS, amivantamab in combination with lazertinib (a third generation EGFR TKI) showed encouraging preliminary activity, including in patients who had progressed on osimertinib (also a third generation EGFR TKI) [15].

2.4 Adverse Events

In 302 patients with locally advanced or metastatic NSCLC who received amivantamab monotherapy at the approved dosage, the most common (incidence ≥ 20%) adverse reactions were rash, infusion-related reaction, paronychia, musculoskeletal pain, dyspnoea, nausea, oedema, cough, fatigue, stomatitis, constipation, vomiting and pruritus [4].

In 129 patients with locally advanced or metastatic NSCLC with EGFR Ex20ins mutations who had progressed on or after platinum-based chemotherapy and treated with amivantamab, the most common (incidence ≥ 2%) grade 3 or 4 adverse reactions were rash (3.9%), diarrhoea (3.1%), paronychia (3.1%), fatigue (2.3%) and dyspnoea (2.3%) [4]. The most common (incidence ≥ 2%) grade 3 or 4 laboratory abnormalities were decreased lymphocytes, decreased albumin, decreased phosphate, decreased potassium, increased glucose, increased alkaline phosphatase, increased gamma-glutamyl transferase and decreased sodium. Adverse reactions led to amivantamab dose interruption in 78% of patients, dose reduction in 15% and permanent treatment discontinuation in 11% of patients; pneumonia, infusion-related reaction, pneumonitis/ILD, dyspnoea, pleural effusion and rash each led to the discontinuation in ≥ 1% of patients. Serious adverse reactions occurred in 30% of patients, with each of the following reactions reported in ≥ 2% of patients: pulmonary embolism, pneumonitis/ILD, dyspnoea, musculoskeletal pain, pneumonia and muscular weakness. Fatal adverse reactions occurred in two patients, one due to pneumonia and another due to sudden death. Clinically relevant adverse reactions occurring in < 10% of amivantamab recipients included ocular toxicity, pneumonitis/ILD and toxic epidermal necrolysis [4].

2.5 Immunogenicity

In CHRYSALIS, 3 of 286 (1%) evaluable amivantamab recipients had treatment-emergent anti-drug antibodies (ADA) with titers of ≤ 1:40 [4]. Available data are insufficient to determine the effect of ADA on the pharmacokinetics, safety or efficacy of amivantamab.

2.6 Companion Diagnostic

The US FDA has approved Guardant360® CDx, a next generation sequencing-based liquid biopsy test, as the companion diagnostic for amivantamab for detecting EGFR Ex20ins mutations in patients with advanced NSCLC [5].

2.7 Ongoing Clinical Trials

An open-label, randomized, multinational, phase III trial (PAPILLON) is comparing the efficacy of amivantamab plus chemotherapy (carboplatin plus pemetrexed) versus chemotherapy alone as a first-line therapy in patients with NSCLC and EGFR Ex20ins mutations [16]. Another open-label, randomized, multinational phase III trial (MARIPOSA) is comparing the efficacy of amivantamab plus lazertinib versus osimertinib alone and versus lazertinib alone as a first-line therapy in patients with advanced, EGFR-mutant NSCLC [17]. The CHRYSALIS trial is ongoing; furthermore, a phase I/Ib trial (CHRYSALIS -2) is evaluating amivantamab

plus lazertinib in Japanese patients with advanced, EGFR-mutant NSCLC [18]. A phase I trial (NCT04606381) is evaluating subcutaneous amivantamab in patients with solid tumours.

3 Current Status

Amivantamab received its first approval on 21 May 2021 in the USA for the treatment of adult patients with locally advanced or metastatic NSCLC harbouring EGFR Ex20ins mutations, as detected by an US FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy [19].

Declarations

Funding The preparation of this review was not supported by any external funding.

Authorship and Conflict of interest During the peer review process the manufacturer of the agent under review was offered an opportunity to comment on the article. Changes resulting from any comments received were made by the authors on the basis of scientific completeness and accuracy. Yahiya. Y. Syed is a salaried employee of Adis International Ltd/Springer Nature, and declares no relevant conflicts of interest. All authors contributed to the review and are responsible for the article content.

Ethics approval, Consent to participate, Consent to publish, Availability of data and material, Code availability Not applicable.

References

1. Neijssen J, Cardoso RMF, Chevalier KM, et al. Discovery of amivantamab (JNJ-61186372), a bispecific antibody targeting EGFR and MET. J Biol Chem. 2021. https://doi.org/10.1016/j.jbc.2021.100641.
2. Moores SL, Chiu ML, Bushey BS, et al. A novel bispecific antibody targeting EGFR and cMet is effective against EGFR inhibitor-resistant lung tumors. Cancer Res. 2016;76(13):3942–53.
3. Grugan KD, Dorn K, Jarantow SW, et al. Fc-mediated activity of EGFR x c-Met bispecific antibody JNJ-61186372 enhanced killing of lung cancer cells. MAbs. 2017;9(1):114–26.
4. Janssen Biotech Inc. RYBREVANT (amivantamab-vmjw) injection, for intravenous use: US prescribing information. 2021. https://www.accessdata.fda.gov/. Accessed 11 Jun 2021.
5. US Food & Drug Administration. FDA approves first targeted therapy for subset of non-small cell lung cancer [media release]. https://www.fda.gov/. 21 May 2021.
6. Guardant Health. Guardant Health announces collaboration with Janssen to develop liquid biopsy companion diagnostic [media release]. www.guardanthealth.com. 8 Jul 2020.
7. Halozyme Therapeutics. Halozyme Therapeutics enters a global collaboration with janssen to develop and commercialize subcutaneous products using ENHANZE™ technology. [media release]. http://www.halozyme.com. 17 Dec 2014.
8. Halozyme Therapeutics. United States Securities and Exchange Commission Form 10-Q. 2020. https://www.sec.gov/. 10 Jun 2021.
9. Genmab AS. Genmab enters broad collaboration with Janssen Biotech, Inc. for DuoBody platform [media release]. http://www.genmab.com. 12 Jul 2012.
10. Genmab. Genmab announces expansion of DuoBody platform collaboration with Janssen Biotech, Inc [media release]. http://www.genmab.com. 4 Dec 2013.
11. Vijayaraghavan S, Lipfert L, Chevalier K, et al. Amivantamab (JNJ-61186372), an Fc enhanced EGFR/cMet bispecific antibody, induces receptor downmodulation and antitumor activity by monocyte/macrophage trogocytosis. Mol Cancer Ther. 2020;19(10):2044–56.
12. Yun J, Lee SH, Kim SY, et al. Antitumor activity of amivantamab (JNJ-61186372), an EGFR-MET bispecific antibody, in diverse models of EGFR Exon 20 insertion-driven NSCLC. Cancer Discov. 2020;10(8):1194–209.
13. Lee SH, Yun J, Jeong SY, et al. JNJ-61186372, a novel EGFR/c-Met bispecific antibody, exhibits potent antitumor activity in broad-spectrum of acquired resistance to EGFR-TKIs [abstract no. 5198]. Cancer Res. 2020;80(16 Suppl).
14. Sabari JK, Shu CA, Park K, et al. Amivantamab in post-platinum EGFR Exon 20 insertion mutant non-small cell lung cancer [abstract no. OA04.04]. J Thorac Oncol. 2021;16(3 Suppl):S108–9.
15. Cho BC, Lee KH, Cho EK, et al. Amivantamab (JNJ-61186372), an EGFR-MET bispecific antibody, in combination with lazertinib, a 3rd-generation tyrosine kinase inhibitor (TKI), in advanced EGFR NSCLC [abstract no. 1258O]. Ann Oncol. 2020;31(4 Suppl):S813.
16. Agrawal T, Artis E, Xie J, et al. PAPILLON: randomized phase 3 study of amivantamab plus chemotherapy vs chemotherapy alone in EGFR Exon20ins NSCLC [abstract no. P76.74]. J Thorac Oncol. 2021;16(3 Suppl):S621.
17. Shreeve SM, Martinez M, Verheijen RB, et al. MARIPOSA: randomized phase 3 study of first-line amivantamab + lazertinib vs osimertinib vs lazertinib in EGFR-mutant NSCLC [abstract no. P76.73]. J Thorac Oncol. 2021;16(3 Suppl):S620–1.
18. Goto K, Hida T, Funami N, et al. A phase 1/1b study of lazertinib as monotherapy and in combination with amivantamab in advanced EGFR-Mutated NSCLC [abstract no. P15.03]. J Thorac Oncol. 2021;16(3 Suppl):S344–5.
19. US Food & Drug Administration. FDA grants accelerated approval to amivantamab-vmjw for metastatic non-small cell lung cancer [media release]. https://www.fda.gov/. 21 May 2021.