



# New England Journal of Medicine Publishes Results of Ebola Clinical Trial Confirming Superiority of Regeneron's REGN-EB3 to ZMapp in Preventing Ebola Deaths

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*Nearly 90 percent survival for patients who received REGN-EB3 treatment earlier in the course of their disease; 66.5 percent survival among all patients who received REGN-EB3*

[Regeneron Pharmaceuticals, Inc.](#) (NASDAQ: REGN) announced today that the *New England Journal of Medicine* (NEJM) published results from the randomized controlled PALM trial showing that Regeneron's REGN-EB3 and another investigational agent provided the highest overall survival rates among four investigational treatments for Ebola virus disease. Monoclonal antibody treatments REGN-EB3, mAb114 and ZMapp and the small molecule antiviral agent remdesivir were given to a trial population of 681 patients who had Ebola during the ongoing outbreak in the Democratic Republic of the Congo (DRC). REGN-EB3, a triple-antibody cocktail, demonstrated superior efficacy compared to the ZMapp control arm across multiple measures, including the primary endpoint of mortality at day 28 (33.5 percent with REGN-EB3 versus 51.3 percent with ZMapp, p=0.002) and secondary endpoint of reduction of the number of days until the Ebola virus was no longer detected in the bloodstream.

The trial was [stopped in August 2019](#) when preliminary results showed that REGN-EB3 crossed the pre-specified superiority threshold for preventing death compared to ZMapp. Although a second investigational treatment, mAb114, did not meet this statistical threshold, it had notable activity, and the decision was made for these two strongest-performing investigational therapies to continue to be administered to patients in a trial extension phase.

The REGN-EB3 antibodies were created using Regeneron's novel and proprietary *VelocImmune*<sup>®</sup> platform, which utilizes a mouse model with a genetically humanized immune system, and associated *VelociSuite* technologies that allow for harvesting and production of specific human antibodies from these mice. These technologies enable the rapid and efficient generation of multiple fully-human antibodies against targets such as Ebola virus, without requiring the identification and utilization of rare human survivors as sources of such therapeutic antibodies.

"In this study, REGN-EB3 demonstrated a significant survival advantage over another antibody treatment approach, underscoring the importance of antibody selection and design. REGN-EB3 was specifically designed to enhance efficacy, reduce the risk of viral resistance and mitigate against potential virus evolution. Our ability to rapidly create and develop these clinically-effective Ebola-specific antibodies highlights the power and speed of our *VelociSuite* human antibody platforms," said Neil Stahl, Ph.D., Executive Vice President of Research and Development at Regeneron. "We are committed to continuing to provide this important treatment to patients through the PALM trial extension trial and 'compassionate use' until the current outbreak ends. We are also working closely with the U.S. Food and Drug Administration to gain regulatory approval and with U.S. and global health authorities to determine appropriate stockpiling of REGN-EB3, as we believe our triple antibody approach may have particular utility for future outbreaks."

Ebola outbreaks have historically resulted in survival rates as low as 10 percent<sup>1</sup> and there are no approved treatments for the disease. Of all patients given REGN-EB3 in this trial setting, 66.5 percent were alive at day 28, compared to 48.7 percent of patients given ZMapp. Importantly, administration of treatment earlier in the course of disease (when viral loads are typically lower) resulted in dramatically higher survival rates with all four investigational treatments, including 88.8 percent survival at day 28 with REGN-EB3. The greatest reduction in mortality (minus 22.5 percent) across all study groups occurred with REGN-EB3 treatment in patients who were treated later in the course of their disease, when risk of dying from Ebola is greatest.

All patients received optimized supportive care (oSOC), including supportive oral and/or intravenous fluids, electrolyte replacement, maintaining of oxygen status and blood pressure, pain management, and antibiotics and antimalarials as indicated. The paper reported 3 serious adverse events for REGN-EB3, compared to 7 for ZMapp, 9 for remdesivir and 10 for mAb114.

## Comparison of 28-day mortality and days to negative PCR by treatment group

	All patients treated with ZMapp + oSOC (Control arm for mAb114 and Remdesivir cohorts)	Patients treated with mAb114 + oSOC	Patients treated with Remdesivir + oSOC	Patients treated with ZMapp + oSOC after Jan'19 (Control arm for REGN-EB3 cohort) <sup>2</sup>	Patients treated with REGN-EB3 + oSOC

28-day mortality for overall patient pop. (No. deaths/Total No.)	49.7% (84/169)	35.1% (61/174)	53.1% (93/175)	51.3% (79/154)	33.5% (52/155)
Mortality difference vs. ZMapp for overall patient pop. (95% CI)	--	-14.6 * (-25.2 to -1.7)	3.4 (-7.2 to 14.0)	--	-17.8 * (-28.9 to -2.9)
28-day mortality for patients who presented early in disease, based on CtNP>22 stratum <sup>3</sup> (No. deaths/Total No.)	24.5% (24/98)	9.9% (10/101)	29.0% (29/100)	25.8% (23/89)	11.2% (10/89)
Mortality difference vs. ZMapp for patients who presented early in disease (95% CI)	--	-14.6 (-32.4 to -2.6)	4.5 (-9.1 to 19.1)	--	-14.6 (-32.6 to -2.3)
28-day mortality for patients who presented late in disease, based on CtNP£22 stratum (No. deaths/Total No.)	84.5% (60/71)	69.9% (51/73)	85.3% (64/75)	86.2% (56/65)	63.6% (42/66)
Mortality difference vs. ZMapp for patients who presented late in disease (95% CI)	--	-14.6 (-33.0 to -0.5)	0.8 (-15.3 to 17.2)	--	-22.5 (-41.8 to -5.1)
Median no. of days to virus clearance (indicated by first negative PCR)	27	16	>28	27	15

\*Statistically significant according to interim monitoring boundary of p<0.034 and p<0.029 for mAb114 and REGN-EB3, respectively.

"This trial required an incredible level of cooperation from international government agencies, non-governmental organizations and drug developers in order to deliver experimental treatments to remote, violence-plagued areas of the DRC," said Sumathi Sivapalasingam, M.D., Senior Director, Early Clinical Development and Experimental Sciences at Regeneron. "Healthcare workers in the field risked their lives to treat patients, all while conducting scientifically rigorous and ethically sound research that will improve the treatment of Ebola in future outbreaks. We are so grateful for their work and that REGN-EB3 was able to improve survival for people suffering from this terrible disease."

#### About the PALM Trial

The PAmoja TuLinde Maisha (PALM ["together save lives" in Kiswahili]) clinical trial was a randomized, multicenter, controlled trial initiated in 2018 to evaluate the safety and efficacy of three investigational Ebola virus disease therapies: mAb114, remdesivir and ZMapp. The trial protocol was amended after the World Health Organization (WHO) held an Ad-Hoc Expert Consultation to assess all preclinical and clinical data on available investigational products, and recommended the addition of REGN-EB3 as a fourth treatment arm. The National Institutes of Health (NIH) and the Institut National de Recherche Biomédicale (INRB) in the DRC jointly sponsored and served as co-principal investigators and are senior authors of the *New England Journal of Medicine* publication.

#### About REGN-EB3

REGN-EB3 (also known as REGN3470-3471-3479) was invented by Regeneron using its *VelociSuite*<sup>®</sup> technologies, starting with the *VelocImmune*<sup>®</sup> mouse; the therapy combines three fully-human monoclonal antibodies. REGN-EB3 has received Orphan Drug designation from both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency; in early September 2019, REGN-EB3 also received Breakthrough Therapy designation from the FDA. REGN-EB3 is being developed, tested and manufactured through contracts awarded in 2015 and 2017 by the Biomedical Advanced Research and Development Authority (BARDA), under the Assistant Secretary for Preparedness and Response within the U.S. Department of Health and Human Services (USG Contract No. HHSO100201500013C and HHSO100201700016C). REGN-EB3 is currently under clinical development and its safety and efficacy have not been fully evaluated by any regulatory authority.

Regeneron's rapid response infectious disease platform has the potential to accelerate response to future epidemics and pandemics that may pose a threat to public health. Regeneron and BARDA have several ongoing research collaborations in addition to the Ebola program, including efforts to develop antibodies targeting up to 10 pathogens that pose significant risk to public health.

#### About Regeneron

Regeneron (NASDAQ: REGN) is a leading biotechnology company that invents life-transforming medicines for people with serious diseases. Founded and led for 30 years by physician-scientists, our unique ability to repeatedly and consistently translate science into medicine has led to seven FDA-approved treatments and numerous product candidates in development, all of which were homegrown in our laboratories. Our medicines and pipeline are designed to help patients with eye diseases, allergic and inflammatory diseases, cancer, cardiovascular and metabolic diseases, infectious diseases, pain and rare diseases.

Regeneron is accelerating and improving the traditional drug development process through our proprietary *VelociSuite*<sup>®</sup> technologies, including *VelocImmune*<sup>®</sup> which uses a unique genetically-humanized mouse to produce optimized fully-human antibodies and bispecific antibodies, and through ambitious research initiatives such as the Regeneron Genetics Center, which is conducting one of the largest genetics sequencing efforts in the world.

For additional information about the company, please visit [www.regeneron.com](http://www.regeneron.com) or follow @Regeneron on Twitter.

## **Regeneron Forward-Looking Statements and Use of Digital Media**

*This press release includes forward-looking statements that involve risks and uncertainties relating to future events and the future performance of Regeneron Pharmaceuticals, Inc. ("Regeneron" or the "Company"), and actual events or results may differ materially from these forward-looking statements. Words such as "anticipate," "expect," "intend," "plan," "believe," "seek," "estimate," variations of such words, and similar expressions are intended to identify such forward-looking statements, although not all forward-looking statements contain these identifying words. These statements concern, and these risks and uncertainties include, among others, the nature, timing, and possible success and therapeutic applications of Regeneron's products, product candidates, and research and clinical programs now underway or planned, including without limitation Regeneron's potential antibody therapy for the treatment of Ebola (REGN-EB3 or REGN3470-3471-3479); the extent to which the results from the research and development programs conducted by Regeneron or its collaborators may be replicated in later studies and lead to therapeutic applications; unforeseen safety issues and possible liability resulting from the administration of products and product candidates in patients, including without limitation Regeneron's potential antibody therapy for the treatment of Ebola; serious complications or side effects in connection with the use of Regeneron's products and product candidates (such as Regeneron's potential antibody therapy for the treatment of Ebola) in clinical trials; the likelihood, timing, and scope of possible regulatory approval and commercial launch of Regeneron's late-stage product candidates and new indications for marketed products; the availability and extent of reimbursement of the Company's products from third-party payers, including private payer healthcare and insurance programs, health maintenance organizations, pharmacy benefit management companies, and government programs such as Medicare and Medicaid; coverage and reimbursement determinations by such payers and new policies and procedures adopted by such payers; ongoing regulatory obligations and oversight impacting Regeneron's marketed products, research and clinical programs, and business, including those relating to patient privacy; determinations by regulatory and administrative governmental authorities which may delay or restrict Regeneron's ability to continue to develop or commercialize Regeneron's products and product candidates, such as Regeneron's potential antibody therapy for the treatment of Ebola; competing drugs and product candidates that may be superior to Regeneron's products and product candidates; uncertainty of market acceptance and commercial success of Regeneron's products and product candidates and the impact of studies (whether conducted by Regeneron or others and whether mandated or voluntary) on the commercial success of Regeneron's products and product candidates; the ability of Regeneron to manufacture and manage supply chains for multiple products and product candidates; the ability of Regeneron's collaborators, suppliers, or other third parties (as applicable) to perform manufacturing, filling, finishing, packaging, labeling, distribution, and other steps related to Regeneron's products and product candidates; unanticipated expenses; the costs of developing, producing, and selling products; the ability of Regeneron to meet any of its financial projections or guidance and changes to the assumptions underlying those projections or guidance; the potential for any license or collaboration agreement, including Regeneron's agreements with Sanofi, Bayer, and Teva Pharmaceutical Industries Ltd. (or their respective affiliated companies, as applicable), as well as the agreements with the Biomedical Advanced Research and Development Authority of the U.S. Department of Health and Human Services referenced in this press release, to be cancelled or terminated without any further product success; and risks associated with intellectual property of other parties and pending or future litigation relating thereto (including without limitation the patent litigation and other related proceedings relating to Dupixent® (dupilumab) and Praluent® (alirocumab)), other litigation and other proceedings and government investigations relating to the Company and/or its operations, the ultimate outcome of any such proceedings and investigations, and the impact any of the foregoing may have on Regeneron's business, prospects, operating results, and financial condition. A more complete description of these and other material risks can be found in Regeneron's filings with the United States Securities and Exchange Commission, including its Form 10-K for the year ended December 31, 2018 and its Form 10-Q for the quarterly period ended September 30, 2019. Any forward-looking statements are made based on management's current beliefs and judgment, and the reader is cautioned not to rely on any forward-looking statements made by Regeneron. Regeneron does not undertake any obligation to update publicly any forward-looking statement, including without limitation any financial projection or guidance, whether as a result of new information, future events, or otherwise.*

*Regeneron uses its media and investor relations website and social media outlets to publish important information about the Company, including information that may be deemed material to investors. Financial and other information about Regeneron is routinely posted and is accessible on Regeneron's media and investor relations website (<http://newsroom.regeneron.com>) and its Twitter feed (<http://twitter.com/regeneron>).*

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<sup>1</sup> "Ebola virus disease." World Health Organization. <https://www.who.int/en/news-room/fact-sheets/detail/ebola-virus-disease>. Last accessed November 26, 2019.

<sup>2</sup> Administration of remdesivir, mAb114 and ZMapp began in November 2018, and REGN-EB3 was added as a fourth arm of the trial in January 2019. Therefore, outcomes in the remdesivir and mAb114 arms and outcomes in the REGN-EB3 arm were compared to slightly different cohorts of participants in the ZMapp control group based on time of enrollment. Overall mortality was very similar in each control group.

<sup>3</sup> CtNP refers to "cycle threshold for the nucleoprotein gene," a measure to determine viral load in the bloodstream. Patients with higher viral loads will have lower CtNP values. Viral load generally increases over time without treatment.

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