

## **Role of the U.S. Federal Government in the Development of GS-5734/Remdesivir**

KEI Briefing Note 2020:1. Kathryn Ardizzone. Updated March 25, 2020.

One of the candidates for treatment of the novel coronavirus (Covid-19) is remdesivir, an antiviral drug that is owned by Gilead Sciences (Gilead). Many of the recent news reports and press releases discussing remdesivir as a candidate for treating Covid-19 state that the compound was developed by Gilead. In a press briefing this month, Gilead Chairman and CEO Daniel O'Day said the following:

"I'm really pleased to say that there's an advanced investigational medicine called remdesivir that Gilead has been working on now for a decade. Spent really billions of dollars trying to develop this medicine that we are in late stage clinical trials with now, in both the United States and China and soon to be other countries[.]"<sup>1</sup>

The research outlined below demonstrates how the U.S. Army, the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH)/National Institute Allergies and Infectious Diseases (NIAID) subsidized the preclinical and clinical development of remdesivir (also referred to as GS-5734).

### **Discovery and Preclinical Research**

The preclinical research on remdesivir began after the Ebola virus outbreak in West Africa in 2014, which accelerated efforts to identify and develop antiviral drugs to combat the disease.

Scientists with the CDC screened possible candidates to treat the Ebola virus from a library (apparently owned by Gilead) of approximately 1,000 compounds "harnessed from over 2 decades of research across multiple antiviral programs."<sup>2</sup> They identified a precursor to GS-5734, which Gilead scientists and researchers with the United States Army Medical Research Institute of Infectious Diseases (USAMRIID) refined and further developed.<sup>3</sup>

USAMRIID scientists tested the effectiveness of GS-5734 against several pathogens, including the Ebola virus, in cell cultures and Rhesus monkeys, in a USAMRIID laboratory. One-hundred percent of monkeys who were treated with GS-5734 three days after being infected with Ebola virus survived the disease.<sup>4</sup>

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<sup>1</sup> <https://catalyst.phrma.org/icymi-continued-biopharmaceutical-action-on-covid-19>.

<sup>2</sup> Siegel et al., "Discovery and Synthesis of a Phosphoramidate Prodrug of a Pyrrolo[2,1-f][triazin-4-amino] Adenine C-Nucleoside (GS-5734) for the Treatment of Ebola and Emerging Viruses," *J Med Chem.* 2017 Mar 9;60(5):1648-1661. doi: 10.1021/acs.jmedchem.6b01594.

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[https://web.archive.org/web/20161224000431/http://www.usamriid.army.mil/press\\_releases/Travis%20ID%20Week%20FINAL.pdf](https://web.archive.org/web/20161224000431/http://www.usamriid.army.mil/press_releases/Travis%20ID%20Week%20FINAL.pdf).

<sup>4</sup> [https://www.usamriid.army.mil/press\\_releases/Travis\\_NATURE\\_2016\\_FINAL.pdf](https://www.usamriid.army.mil/press_releases/Travis_NATURE_2016_FINAL.pdf).

Although the focus of the study was on the drug's effect in the Ebola virus, it laid the groundwork for developing remdesivir as a possible treatment for the coronavirus. An article reporting the results of the [study](#) states that "the broad-spectrum antiviral activity of GS-5734 *in vitro* against other pathogenic RNA viruses, including filoviruses, arenaviruses, and **coronaviruses**, suggests the potential for wider medical use."<sup>5</sup> The study was supported by "[t]he Joint Science and Technology Office for Chemical and Biological Defense (JSTO-CBD) of the Defense Threat Reduction Agency (DTRA) under plan #CB10218" and NIH Grant No. R01AI113321.<sup>6</sup> R01AI113321 is a NIAID grant to Rachel Fearn with Boston University for a total of \$1,659,997.<sup>7</sup>

CDC and USAMRIID played an important role in the discovery of remdesivir: "The partnership with government organizations, including CDC and USAMRIID, that generated the screening data and conducted the rhesus efficacy studies was critical to the successful identification of [remdesivir]."<sup>8</sup>

The results of the Rhesus monkey study led scientists with the University of North Carolina - Chapel Hill, Vanderbilt, and Gilead (coordinated by the Antiviral Drug Discovery and Development Center, or AD3C) to investigate GS-5734 as a candidate for treating Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS), which are caused by coronaviruses.<sup>9</sup> More specifically, COVID-19 belongs to the [Betacoronavirus](#) genre of the Coronaviridae family, which includes SARS-CoV and Middle East respiratory syndrome CoV (MERS-CoV).<sup>10</sup>

The scientists found that the compound prevents replication in a wide range of coronaviruses in human lung cells and that it is effective against SARS-CoV in mice. This research was funded by the following NIH grants:

- U19 AI109761, a NIAID grant to Columbia University for a total of \$32,615,935;
- R01 AI108197, a NIAID grant to Vanderbilt University for a total of \$4,235,454;
- R01 AI132178, a NIAID grant to UNC-Chapel Hill for a total of \$3,788,580;
- P30 DK065988, a "Center Core Grant" to UNC-Chapel Hill; and

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<sup>5</sup> Warren, Travis K et al. "Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys." *Nature* vol. 531,7594 (2016): 381-5. doi:10.1038/nature17180 (emphasis added).

<sup>6</sup> *Id.*

<sup>7</sup> The NIH RePORTER database ([projectreporter.nih.gov](http://projectreporter.nih.gov)) does not always indicate what portion of the grant awards was dedicated exclusively to remdesivir research and development.

<sup>8</sup> Siegel et al., "Discovery and Synthesis of a Phosphoramidate Prodrug of a Pyrrolo[2,1-f][triazin-4-amino] Adenine C-Nucleoside (GS-5734) for the Treatment of Ebola and Emerging Viruses," *J Med Chem.* 2017 Mar 9;60(5):1648-1661. doi: 10.1021/acs.jmedchem.6b01594.

<sup>9</sup> Sheahan, Timothy P et al. "Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses." *Science translational medicine* vol. 9,396 (2017): eaal3653. doi:10.1126/scitranslmed.aal3653.

<sup>10</sup> Ko et al., "Arguments in favour of remdesivir for treating SARS-CoV-2 infections," *International Journal of Microbial Agents*, 2020 Mar 6, <https://doi.org/10.1016/j.ijantimicag.2020.105933/>.

- U19 AI109680, a grant to the University of Alabama for a total of \$34,907,030.

U19AI109680 funded the AD3C. Dr. Richard Whitley, a [professor at UAB](#)<sup>11</sup> and [member of the Board of Directors of Gilead](#),<sup>12</sup> is the principal investigator for this grant.

Next, UNC-Chapel Hill, Vanderbilt, and Gilead scientists performed an investigation showing that remdesivir was more effective than other treatments against MERS-CoV in mice and human cell cultures.<sup>13</sup> The [study](#) was funded by NIAID Grant No. 5R01AI132178 (\$1,166,670).

A later [study](#) of remdesivir in mice showed that the drug inhibits coronavirus replication.<sup>14</sup> This research, performed by scientists with Vanderbilt, UNC-Chapel Hill, and Gilead, as well as the University of the South, was funded by NIH and UNC-Chapel Hill grants: “the Antiviral Drug Discovery and Development Center 5U19AI109680, National Institutes of Health grants R01AI108197 and 5T32AI089554 (M.L.A.), and the UNC Cystic Fibrosis and Pulmonary Diseases Research and Treatment Center (BOUCHE15RO and NIH P30DK065988).”

Grant No. 5T32AI089554 is a NIAID grant to Vanderbilt University totalling \$726,584. The other NIH grants supporting the study were previously described above.

More recently, U.S. scientists investigated remdesivir in MERS-CoV-infected monkeys and found that the drug reduced the severity of the disease, inhibited virus replication, and mitigated damage to the lungs.<sup>15</sup> This research was funded by “the Intramural Research Program of NIAID, NIH, and federal funds from the Biomedical Advanced Research and Development Authority[.]”

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<https://www.uab.edu/news/health/item/11082-investigational-compound-remdesivir-developed-by-uab-and-nih-researchers-being-used-for-treatment-of-novel-coronavirus>.

<sup>12</sup> <https://www.gilead.com/about/leadership/board-of-directors/richard-whitley>.

<sup>13</sup> Sheahan, Timothy P et al. “Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV.” Nature communications vol. 11,1 222. 10 Jan. 2020, doi:10.1038/s41467-019-13940-6.

<sup>14</sup> Agostini, Maria L et al. “Coronavirus Susceptibility to the Antiviral Remdesivir (GS-5734) Is Mediated by the Viral Polymerase and the Proofreading Exoribonuclease.” mBio vol. 9,2 e00221-18. 6 Mar. 2018, doi:10.1128/mBio.00221-18.

<sup>15</sup> De Wit et al., “Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection,” PNAS 13 Feb 2020, <https://doi.org/10.1073/pnas.1922083117>.

Other recent preclinical research on remdesivir was conducted by [Canadian](#)<sup>16</sup> and [Chinese](#)<sup>17</sup> scientists.

The preclinical research discussed above is relevant to the development of remdesivir. A recent [article](#) reviewing remdesivir studies states that the data from these studies “provide preliminary evidence supporting the clinical potential of remdesivir for human infections caused by contemporary and emerging coronaviruses, including SARS-CoV-2.”<sup>18</sup> Because this research was conducted, in large part, by U.S. scientists funded by U.S. taxpayers, it is not accurate to state or imply that remdesivir was developed by Gilead alone.

## Clinical Research

Clinical research on remdesivir began in late 2015 or early 2016, when the compound was administered to a Scottish healthcare worker, [Pauline Cafferkey](#),<sup>19</sup> who contracted Ebola virus during a humanitarian mission in Sierra Leone.<sup>20</sup> The study of remdesivir in Cafferkey was funded by Royal Free London NHS Foundation Trust. Gilead provided the GS-5734 free of charge through its compassionate use program. Remdesivir was also administered to an infant born with the Ebola virus through Gilead’s compassionate use program.

From July 1, 2016 to October 7, 2019, GS-5734 was investigated in humans in Clinical Trial No. [NCT02818582](#), “GS-5734 to Assess the Antiviral Activity, Longer-Term Clearance of Ebola Virus, and Safety in Male Ebola Survivors With Evidence of Ebola Virus Persistence in Semen.” This clinical trial was sponsored by the National Institute of Allergy and Infectious Diseases (NIAID).

From November 20, 2018, to August 9, 2019, 681 patients with Ebola were enrolled in Clinical Trial No. [NCT03719586](#), “Investigational Therapeutics for the Treatment of People With Ebola Virus Disease.” The patients were administered four different treatments in centers across the Democratic Republic of Congo. Remdesivir was administered to 175 of the patients, and no serious adverse side effects were reported. The trial was funded:

primarily by the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH). In-kind support and cosponsorship were provided by the national government of the Democratic Republic of Congo (DRC) and the African Coalition for Epidemic Research,

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<sup>16</sup> Gordon et al., “The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus,” *Journal of Biological Chemistry* 24 Feb. 2020, doi: 10.1074/jbc.AC120.013056.

<sup>17</sup> Al-Tawfiq et al., “Remdesivir as a possible therapeutic option for the COVID-19,” *Travel Medicine and Infectious Diseases* 5 Mar 2020 <https://doi.org/10.1016/j.tmaid.2020.101615>.

<sup>18</sup> Ko et al., “Arguments in favour of remdesivir for treating SARS-CoV-2 infections,” *International Journal of Microbial Agents*, 2020 Mar 6, <https://doi.org/10.1016/j.ijantimicag.2020.105933/>.

<sup>19</sup> [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(16\)30369-5/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(16)30369-5/fulltext).

<sup>20</sup> Jacobs, Michael et al. “Late Ebola virus relapse causing meningoencephalitis: a case report.” *Lancet* (London, England) vol. 388,10043 (2016): 498-503. doi:10.1016/S0140-6736(16)30386-5.

Response, and Training. Logistic support was provided by the World Health Organization (WHO). Some funding for NIAID was provided by the National Cancer Institute through a contract (HHSN261200800001E) with Leidos Biomedical Research and subcontracts to the Mitchell Group. The Biomedical and Advanced Research and Development Authority of the U.S. Department of Health and Human Services provided financial support for the production of ZMapp (contract number, HHSO100201400009C) and REGN-EB3 (contract number, HHSO100201700016C). NIAID and the Defense Advanced Research Projects Agency of the U.S. Department of Defense provided financial support for the production and provision of MAb114. Mapp Biopharmaceutical provided ZMapp, Gilead Sciences provided remdesivir, and NIAID provided MAb114 to the project. Regeneron Pharmaceuticals provided financial support for the provision of REGN-EB3 to the project.<sup>21</sup>

In its SEC 10-k filings for the years ending in 2015 and 2016, Gilead reported that it was investigating GS-5734 in healthy human volunteers to establish the drug’s safety; however, a search for “GS-5734” at ClinicalTrials.gov did not yield any results describing a 2015 or 2016 trial of the compound that was sponsored by Gilead.

Gilead pursued a path to FDA approval of remdesivir under the FDA’s Animal Rule, in which the FDA may rely on efficacy findings from animal studies of a drug in cases where it is not feasible or ethical to conduct human trials.

After the Covid-19 outbreak, a number of clinical trials began investigating remdesivir in patients who contracted the virus. A spreadsheet listing those trials is available [here](#).

## **Timeline**

**2008. April 23.** Gilead files U.S. provisional patent application 61/047,263. This provisional application names Aesop Cho and Choung Kim, Gilead in-house scientists, as co-inventors. This application appears to have claimed the remdesivir compound formula.

### **U.S. members of the 61/047,263 patent family**

application	assignee	priority date	patent	issue date
12/428,234	Gilead	Apr. 23, 2008	8,012,941	09/06/2011
12/428,176	Gilead	Apr. 23, 2008	8,008,264	08/30/2011
13/196,117	Gilead	Apr. 23, 2008	8,318,682	11/27/2012
13/649,511	Gilead	Apr. 23, 2008	8,853,171	10/07/2014
15/288,271	Gilead	Apr. 23, 2008	RE46,762	03/27/2018

<sup>21</sup> Mulangu, S. et al. A randomized, controlled trial of Ebola virus disease therapeutics. *N. Engl. J. Med.* 381, 2293–2303 (2019), DOI: 10.1056/NEJMoa1910993.

**2014. February 12.** The National Institute of Allergy and Infectious Diseases (NIAID) awards the University of Alabama Birmingham (UAB) U19AI109680, a multi-year grant with a total cost of \$34,907,030 as of March 2020 according to Project REPORTER. The UAB is funding the Antiviral Drug Discovery and Development Center (AD3C) with this grant, which supports preclinical research of remdesivir, as described above. Dr. Richard Whitley, a professor at UAB and member of the [Board of Directors at Gilead](#), is a principal investigator for this grant.

**2015.** Gilead begins investigating GS-5734 for treatment of the Ebola virus in a Phase I study, according to Gilead’s SEC [10-k](#) for 2015.

**2015. Sept 18.** Remdesivir was granted [Orphan status](#) for treatment of Ebola virus.

**2015. Oct 9.** A patent application associated with remdesivir is filed, U.S. Provisional Application No. 62/239,696 filed (“the ‘696 patent application”). The ‘696 patent application is linked to International Application No. PCT/US2016/052092, “Methods for Treating Arenaviridae and Coronaviridae Virus Infections.” PCT/US2016/052092 is listed in an article demonstrating that GS-5734 is a possible treatment for the coronavirus.

**U.S. members of the PCT/US2016/052092 patent family**

application	assignee	priority date	patent	issue date
15/267,433	Gilead	09-16-2015	10,251,904	April 9, 2019
16/265,016	Gilead	09-16-2015	pending	-

Also on this same date, USAMRIID issues a [press release](#) stating that “Rhesus monkeys were completely protected from the deadly Ebola virus when treated three days after infection with a compound that blocks the virus’s ability to replicate. These encouraging preclinical results suggest the compound, known as GS-5734, should be further developed as a potential treatment[.]”

**2015. Oct 21.** Gilead issues a [press release](#) about GS-5734. Among other things, the press release states that:

- “Gilead provided GS-5734 to a Scottish healthcare worker who contracted the Ebola virus, in fulfillment of a compassionate use request.”
- “GS-5734 was discovered as part of Gilead’s program to screen compounds in its libraries for activity against a range of potential emerging viruses, including Ebola. In collaboration with the Centers for Disease Control and Prevention (CDC) and the United States Army Medical Research Institute of Infectious Diseases (USAMRIID), the company identified GS-5734 in vitro activity against the Ebola virus.”
- “In animal studies conducted at USAMRIID, treatment initiated on day 3 post-infection with Ebola virus resulted in 100 percent survival of monkeys. Data from these studies were recently presented at the annual Interscience Conference of Antimicrobial Agents and Chemotherapy / International Congress of Chemotherapy and Infection



(ICAAC/ICC) meeting and at ID Week. Gilead recently initiated a Phase 1 clinical trial in healthy human volunteers to determine the safety, tolerability and pharmacokinetics of GS-5734.”

**2016.** Gilead’s study of GS-5734 as a treatment for the Ebola virus advances to Phase 2, according to Gilead’s SEC [10-k](#) filing for 2016.

**2016. March 2.** Travis K. Warren (USAMRIID) and other scientists affiliated with USAMRIID, Boston University, and Gilead Sciences publish “Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys” describing a preclinical study of GS-5734 in Rhesus monkeys.

- The “Acknowledgments” section states as follows: “Studies at USAMRIID were in part supported by The Joint Science and Technology Office for Chemical and Biological Defense (JSTO-CBD) of the Defense Threat Reduction Agency (DTRA) under plan #CB10218. Work in the Fearn’s laboratory [Boston University] was supported by NIH R01AI113321.”
- This is the first scientific article published at PubMed that mentions GS-5734.

**2016. March 3.** USAMRIID issues a [press release](#) reporting the preclinical study of remdesivir in Rhesus monkeys described in the March 2, 2016 article. Regarding the development of GS-5734, the press release provides the following information:

- The work is the result of a continuing collaboration between USAMRIID and Gilead Sciences.
- Scientists at the CDC screened compounds from Gilead’s library of compounds to identify the precursor to GS-5734.
- Identifying the precursor to GS-5734 “led to the effort by Gilead and USAMRIID to further refine, develop and profile the compound[.]”
- Led by USAMRIID Science Director Sina Bavari, Ph.D., the paper’s senior author, the research team used cell culture and animal models to demonstrate the compound’s antiviral activity against several pathogens, including Ebola virus.

**2016. July 1.** Start of NCT02818582, “GS-5734 to Assess the Antiviral Activity, Longer-Term Clearance of Ebola Virus, and Safety in Male Ebola Survivors With Evidence of Ebola Virus Persistence in Semen”, a Phase II clinical trial of the compound sponsored by NIAID.

**2016. Sept 16.** Gilead files Patent Application, [15/267,433](#), “Methods for treating arenaviridae and coronaviridae virus infections.” This is the same title as the [International Patent Application](#) listed in “Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses,” which describes preclinical research indicating that “GS-5734 may prove effective against endemic MERS-CoV in the Middle East, circulating human CoV, and possibly most importantly, emerging CoV of the future.”

**2017. June 28.** Researchers publish “Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses” which describes preclinical research indicating that “GS-5734 may prove effective against endemic MERS-CoV in the Middle East, circulating human CoV, and possibly most importantly, emerging CoV of the future.”

- The Acknowledgments section (Funding) states: “We would like to acknowledge the following funding sources, Antiviral Drug Discovery and Development Center (5U19AI109680), grants from the National Institutes of Health ([AI108197](#), [AI109761](#)) and Cystic Fibrosis and Pulmonary Research and Treatment Center (BOUCHE15RO and NIH P30DK065988). Additionally, compound formulation, pharmacokinetic and metabolism studies were performed and paid for by Gilead Sciences.”
- The “Conflicts” section lists “International Application No. PCT/US2016/052092 filed by Gilead Sciences, Inc., directed to methods of treating coronaviridae virus infections.”

**2019. March 28.** USAMRIID issues a [press release](#) stating that the FDA approved a plan for the development of remdesivir as a treatment for Ebola virus under the “Animal rule,” which provides that “for certain products, when obtaining efficacy data from human patients is not ethical or feasible, the FDA may grant approval . . . based on efficacy data from well-controlled studies in adequately characterized animal model(s), when the results of those studies establish that the drug candidate is reasonably likely to produce clinical benefit in humans..”

**2019. Dec 31.** Chinese officials reported an outbreak of pneumonia in the Huanan Seafood Wholesale Market in Wuhan, China.

**2020. Jan 7.** Chinese authorities confirmed that the pneumonia cluster was COVID-19.

**2020. Feb 6.** Start of Clinical Trial No. [NCT04257656](#), “A Phase 3 Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of Remdesivir in Hospitalized Adult Patients With Severe 2019-nCoV Respiratory Disease.” Sponsored by Capital University, a university in China.

**2020. Feb 7.** UAB issues a [press release](#) stating that remdesivir was “developed by UAB and NIH researchers.” This press release acknowledges a “U19” grant to Dr. Richard Whitley, likely the NIH/NIAID grant number U19AI109680. Dr. Whitley is cited stating the following:

“The collaboration between UAB, our colleagues at Southern Research, Vanderbilt University and the University of North Carolina, along with our pharmaceutical partner Gilead Sciences, is indicative of our collaborative approach to respond to outbreaks in real time, and in helping communities worldwide fight 2019-nCoV. This is a prime example of how the research we are conducting at UAB plays a critical role in treating patients on a global scale and our contribution of substantial scientific advances.”



**2020. Feb 6.** Start of NCT04257656, “A Phase 3 Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of Remdesivir in Hospitalized Adult Patients With Severe 2019-nCoV Respiratory Disease.” Sponsor: Capital Medical University (Chinese university).

**2020. Feb 12.** Start of Clinical Trial No. [NCT04252664](#), “A Phase 3 Randomized, Double-blind, Placebo-controlled Multicenter Study to Evaluate the Efficacy and Safety of Remdesivir in Hospitalized Adult Patients With Mild and Moderate 2019-nCoV Respiratory Disease.” Sponsored by Capital Medical University and Chinese Academy of Medical Sciences.

**2020. Feb 21.** Start of Clinical Trial No. [NCT04280705](#), “Adaptive COVID-19 Treatment Trial,” conducted by NIAID.

**2020. March 6.** Start of Clinical Trial No. [NCT04292899](#), “A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Severe COVID-19.” Sponsored by Gilead Sciences.

**2020. March 10.** Start of Clinical Trial No. [NCT04302766](#), “Expanded Access Remdesivir (RDV; GS-5734.™).” Clinical trial of “DoD-affiliated personnel (including active and reserve component service members, US civilian employees, contractors, other US personnel, and dependents of any age, as well as allied military forces and local nationals) who have been granted access to the medical facility[.]” sponsored by USAMRIID.

**2020. March 15.** Start of Clinical Trial No. [NCT04292730](#) “A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Moderate COVID-19 Compared to Standard of Care Treatment[.]” Sponsored by Gilead.