Remdesivir: The search for an effective treatment for COVID-19

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EMA workshop on primary efficacy endpoints for antivirals and monoclonal antibodies intended to treat COVID-19 and Influenza
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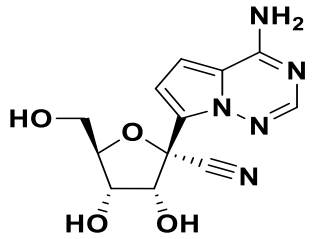
Disclaimer

- YM is an employee of Gilead Sciences.
- Remdesivir is not approved for the treatment of filovirus infections.

Remdesivir is a broad-spectrum antiviral agent

Gilead library of nucleosides and nucleotides

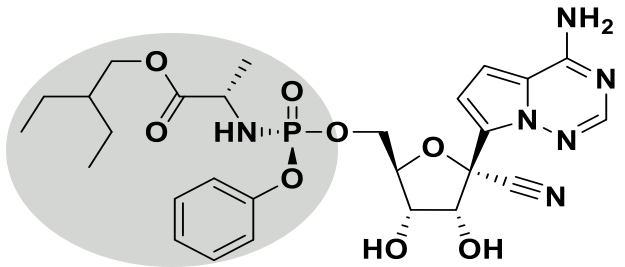
Screening



GS-441524

Prodrug design

Profiling



Remdesivir

Virus Family	Virus	EC_{50} (µM)
Filoviruses	Ebola (Makona)	0.19
	Ebola (Kikwit)	0.14
	Bundibugyo	0.19
	Sudan	0.24
	Marburg	0.06
Coronaviruses	MERS	0.07
	SARS	0.07
Paramyxoviruses	Nipah	0.05
	Measles	0.04
	Hendra	0.06
Bunyaviruses	CCHF	>50
Togaviruses	Chikungunya	>20

Warren TK, et al. Nature 2016;531:381-5.

Lo MK, et al. Sci Reports 2017;7:43395.

Sheahan TP, et al. Sci Transl Med 2017.

Over a decade of work on remdesivir supported Gilead's response to the COVID-19 pandemic

Status of Remdesivir in January 2020:

- Ph1 program: n = 86
- Ebola outbreaks: n = ~300
- Pan-CoV activity established
- Optimized lyophilized drug formulation
- 5,000 treatment regimens available

RSV activity

Ebola activity

Ph1 studies started

Ebola emergency use

Pan-filovirus activity

Ebola clinical testing started

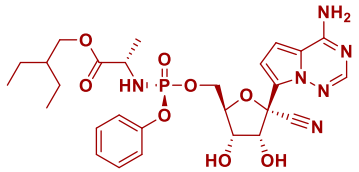
Ebola in West Africa

Ebola in DRC

2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | 2021 | 2022 | 2023 | 2024

COVID-19 Pandemic

Remdesivir isolated



MERS-CoV SARS-CoV activity

SARS-CoV in vivo efficacy

MERS-CoV in vivo efficacy

Pan-CoV activity

Veklury® remdesivir 100 MG FOR INJECTION

FDA approval for COVID-19

>14 million treated with remdesivir

>170 countries with remdesivir access

Warren et al. Nature 2016
Siegel et al. J Med Chem 2017
Lo et al. Sci Reports 2017
Sheahan et al. Sci Transl Med 2017
Brown et al. Antiviral Res 2019
Sheahan et al. Nature Comm 2019
Mulangu et al, NEJM 2019
De Wit et al. PNAS 2020
Lo et al. PNAS 2020
Williamson et al. Nature 2020
Pruijssers et al. Cell Reports, 2020
Xie et al. Nature Comm, 2020
Porter et. al. J Infect Dis 2020
Mackman et al. J Med Chem 2021
Cross et. al. Nature Comm 2021
Cross et. al. JCI Insight 2022

Remdesivir clinical development for COVID-19

Jan 10
China CDC identifies novel CoV as cause of pneumonia

Jan 31
10K cases
200 deaths

Mar 11
WHO declares pandemic

Mar 31
875K cases
44K deaths

May 31
6.2M cases
375K deaths

July 31
18M cases
675K deaths

Sept 30
34M cases
1.0M deaths

Nov 30
> 60M cases
1.5M deaths

Jan | Feb | Mar | Apr | May | June | July | Aug | Sept | Oct | Nov | Dec

Jan 26
First Gilead CU patient dosed in U.S.

Jan 31
NEJM : first U.S. case on RDV

Feb 6
China severe COVID trial initiated

Feb 21
NIAID ACTT-1 trial initiated

Mar 6
Gilead Simple severe trial initiated

Mar 15
Gilead Simple moderate trial initiated

April 10
NEJM: RDV CU case series

May 1
EUA in US granted

May 7
Approval in Japan

May 22
NEJM: ACTT-1 interim data

May 27
NEJM: Gilead SIMPLE severe study

June 15
CARAVAN Gilead pediatric study initiated

July 3
CMA in EU granted

Aug 21
JAMA: Gilead Simple moderate study

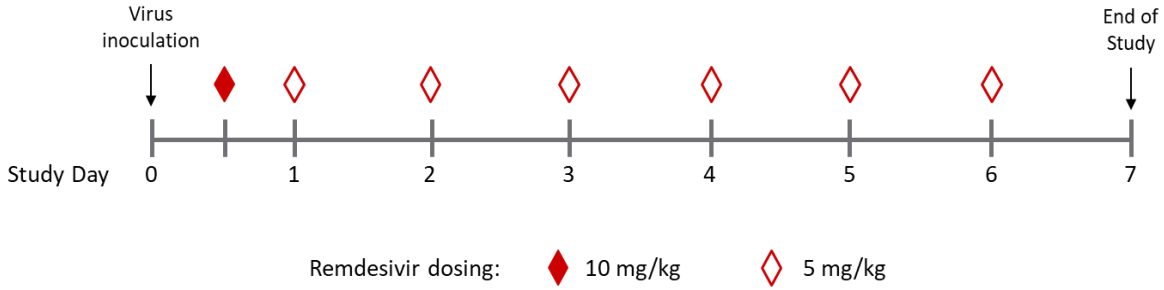
Oct 08
NEJM: ACTT-1 Final data

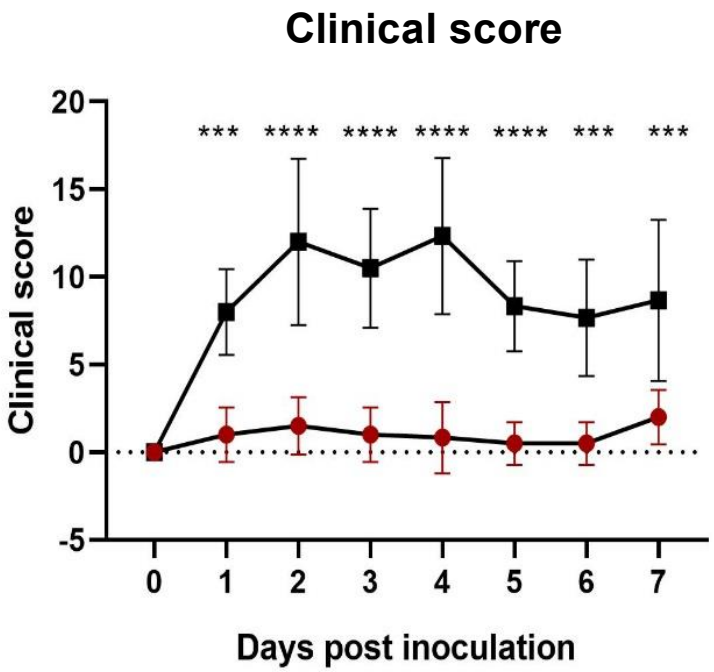
Oct 22
FDA approval of Veklury®

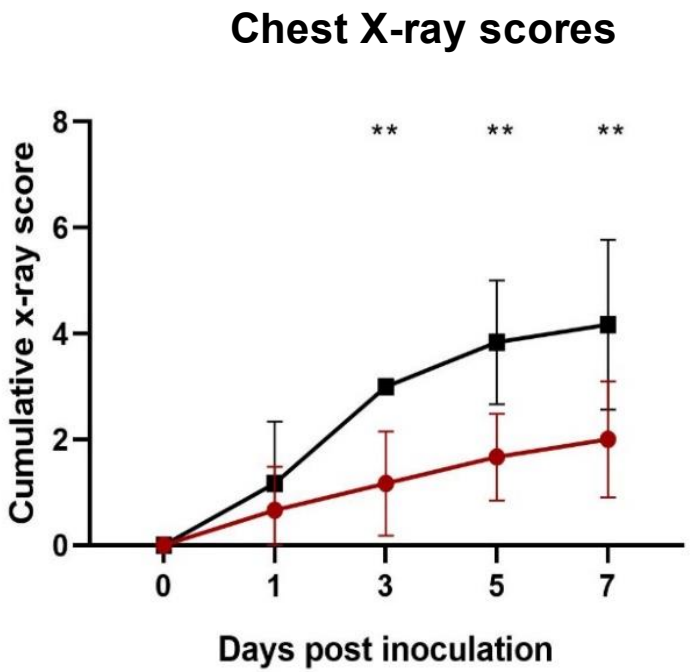
Nov 19
US EUA granted for remdesivir+ baricitinib combination

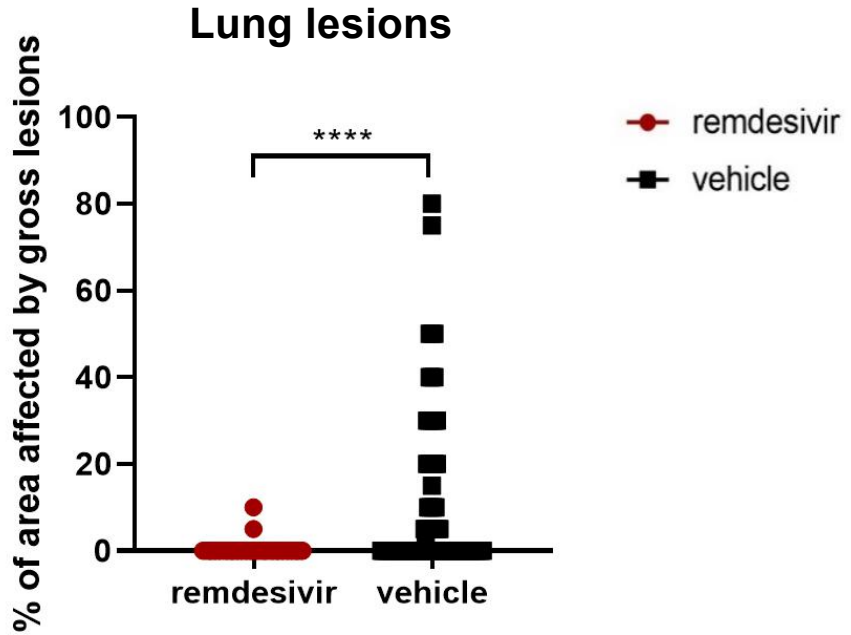
Remdesivir in SARS-CoV-2 infected rhesus monkeys

- NIH Rocky Mountain Lab, Montana
- Rhesus inoculated with SARS-CoV-2 (IT, IN, IO, oral)
- Treatment initiated 12 hrs after infection









** P < 0.01, *** P < 0.001, **** P < 0.0001

Williamson et al., Nature, 2020

Remdesivir: supply and production

Supply

- January: ~ 5,000 treatment courses
- December: Able to meet global demand

Expansion of production capacity

- Process improvements have shortened manufacturing timelines significantly
- Consortium of pharmaceutical and chemical manufacturing companies
- License to 9 generic drug companies to supply 127 low/middle income countries

Production is time-and resource-intensive

- Long, linear chemical synthesis that must be completed sequentially

- Involves novel substances, specialized chemistry and sterile drug manufacturing capabilities

Common Goal: Determine the safety and efficacy of remdesivir as a treatment for COVID-19 and deliver rapid, broad access for appropriate patients

Establish Safety and Efficacy

Generate clinical data to determine utility and support regulatory filings

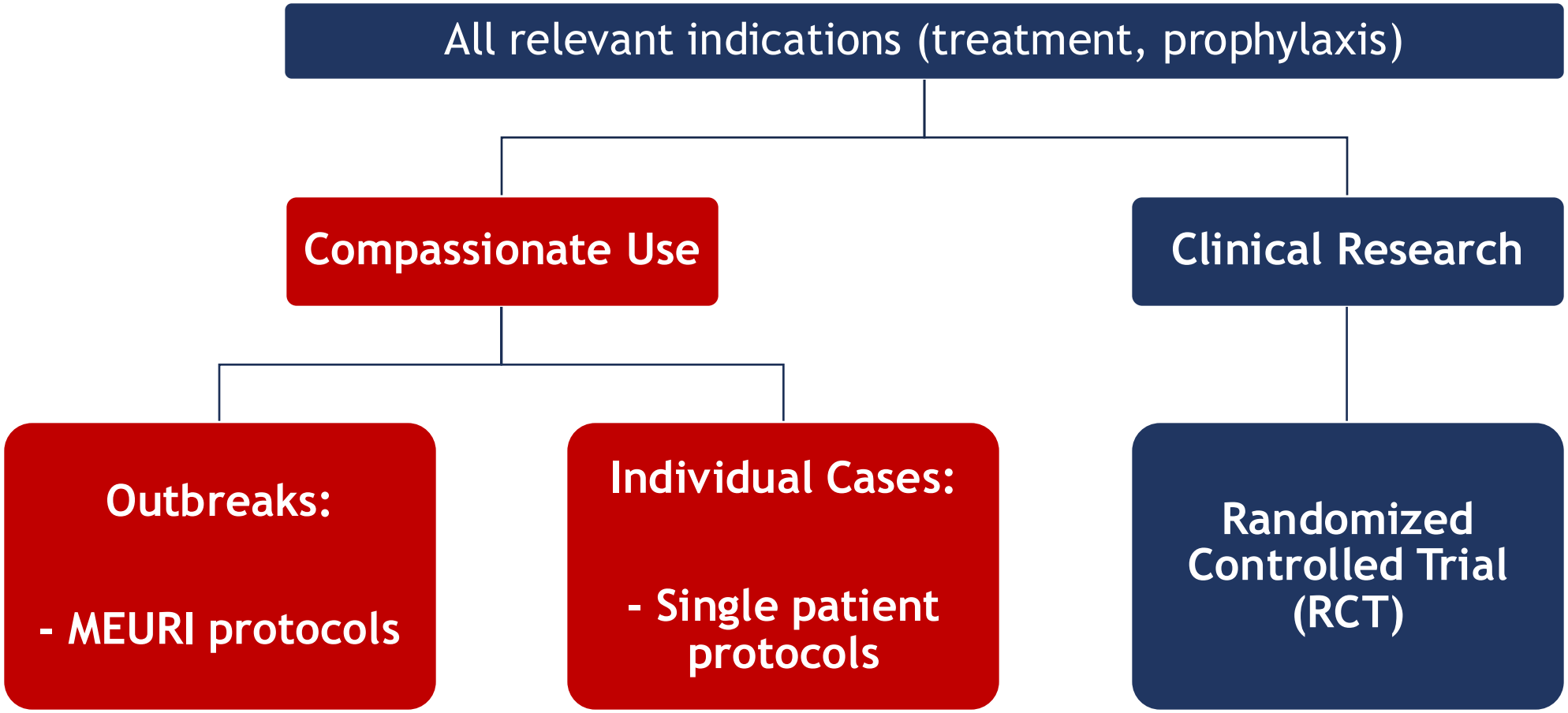
Scale Up Manufacturing

Expand manufacturing to increase product supply ahead of potential increased demand

Deliver Responsible Access

Provide data-driven access that is ethical for each stage of product development

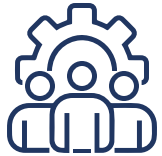
Drug for outbreaks – compassionate use & RCTs



Key characteristics: compassionate use vs. RCT

	Start-up time	HA/EC Review	Single Patient	Outbreaks	Placebo controlled	Registration
Compassionate Use	Shorter	✓	✓ (Single patient)	✓ (MEURI)	✗	✗
RCT	Longer	✓	✗	✓	✓	✓

Gilead Rapid Response Team executes response to outbreaks



Rapid Response Team

Cross-functional group to rapidly and efficiently respond to outbreaks, epidemics, and pandemics

Responsibilities:

- Rapid Response Coordination
- Emergency Response Protocols
- Rapid Drug Supply Deployment
- R&D Coordination
- Strategic Partnerships
- Funding Requests

Gilead response to outbreaks

1

Gilead Rapid Response Team (RRT) activated

- Activation following outbreak notification
- Coordinates activity with local Ministry of Health (MoH) and key stakeholders

2

Determine scope of Gilead response

- MoH Emergency Use Authorization (EUA) vs. compassionate use vs. RCT*
- Protocol/ICF available in advance, if feasible
- Establish key agreements
  - CDAs
  - Contracts
  - CTAs
  - Letters of Agreement

3

Additional considerations

- Import/export permits
- Clinical supply labeling
- Drug shipment
- Chain of custody
- Regulatory approvals

4

Data collection and sharing

- Critical for industry partners
- Overarching goal: labeled indication for prophylaxis and/or treatment

***: Implementation of RCTs during outbreaks (eg, PALM trial) and pandemics (eg, ACTT-1 trial) feasible when key stakeholders (WHO, NIH, MoH, collaborators, others) fully engaged and rapidly aligned**

Summary

- Remdesivir is a broad-spectrum antiviral agent approved for treatment against SARS-CoV2
- Key learnings from Gilead's responses to the COVID-19 pandemic:
  - Long term investments in emerging viruses and public-private partnerships are critical
  - Need for a dedicated Rapid Response Team for agile response to emerging viruses, outbreaks, and pandemics
  - Rapid, efficient leveraging of available data and real-time analytics are critical in a fast-moving environment
  - Cross sector collaboration, proactive response planning, and platform readiness accelerate impact

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Thank you