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# Remdesivir:
## *Clinical Trials and Beyond*


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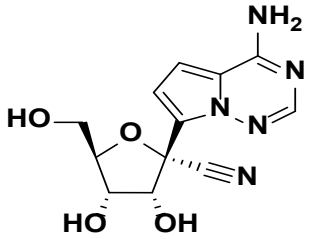
# Remdesivir Is a Broad-spectrum Antiviral Agent

Gilead library of nucleosides and nucleotides

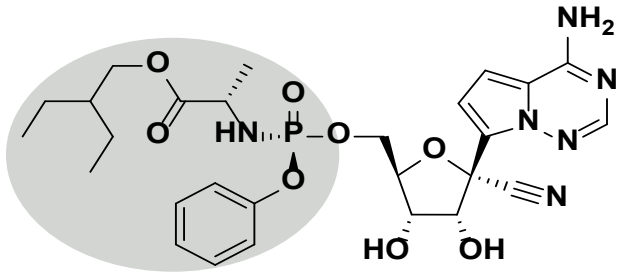
**Screening**



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.*

# Clinical Development of Remdesivir (2015-2019)

**Ph 1 PK/safety studies**

**IND**

**Ebola survivors** (Liberia and Guinea )

**PEP for lab workers** (Hungary, USA)*

**PALM RCT Acute Ebola** (DRC)

***Ebola Outbreak in West Africa***

***Ebola Outbreaks in DRC***

**1st** **2nd**

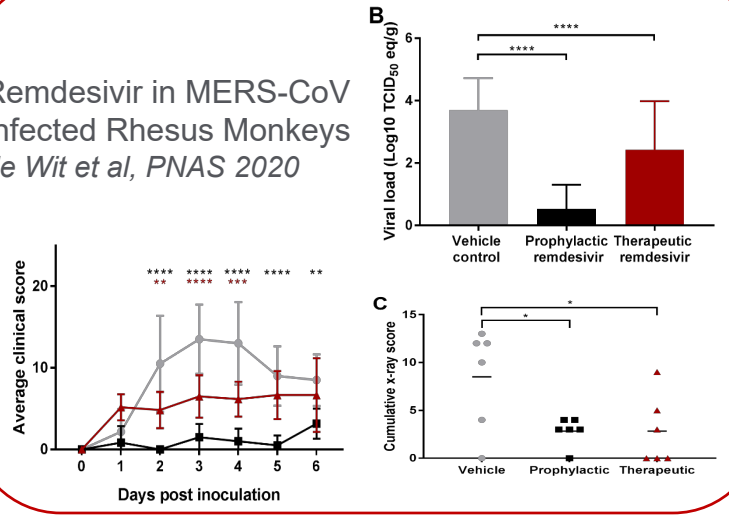
2015 2016 2017 2018 2019

**Meningo Encephalitis** (UK)*

**Neonatal infection** (Guinea)*

**Coronavirus Animal studies initiated**

Remdesivir in MERS-CoV Infected Rhesus Monkeys
*de Wit et al, PNAS 2020*




**Measles** (Belgium)*

**Measles/SSPE** (Latvia)*

**Compassionate use MEURI protocol** (DRC)

DRC, Democratic Republic of Congo; EBOV, Ebola virus; IND, investigational new drug; MEURI, monitored emergency use of unregistered and investigational interventions (WHO); PEP, post-exposure prophylaxis; SSPE, subacute sclerosing panencephalitis; *** single patient compassionate use.**

# Peer Reviewed Published Remdesivir Trials For COVID-19

| Data Source | | N | Hospitalized patients: Moderate No Oxygen | Hospitalized patients: Severe Requiring Oxygen | Hospitalized patients: Critical Intubated | Placebo or Standard of Care | Key Question | Key Findings |
|---|---|---|---|---|---|---|---|---|
| ACTT-1 | Randomized Double blind Placebo controlled | 1063 | ✓ | ✓ | ✓ | P | Is RDV safe and effective treatment for COVID-19 patients? | **RDV superior to PBO in time to recovery with lower mortality among patients on low-flow $O_2$[1]** |
| China Study | Randomized Double blind Placebo controlled | 237 (453 planned) | ✓ | ✓ | ✓ | P | | *Inconclusive; discontinued due to low enrollment —underpowered at 58% Recovery : 21 d (RDV) vs 23 d (placebo) ; HR 1.23)* |
| SIMPLE Severe | Randomized Open label | 400 | | ✓ | | | Is a 5 day treatment course as effective and safe as a 10 day course of RDV? | **Similar 5 day/10 day efficacy in severe COVID-19 (non-mechanically ventilated)[3]** |
| SIMPLE Moderate | Randomized Open label | 600 | ✓ | | | SoC | | **Among hospitalized patients not requiring $O_2$, 5 day treatment superior to SOC[4]** |

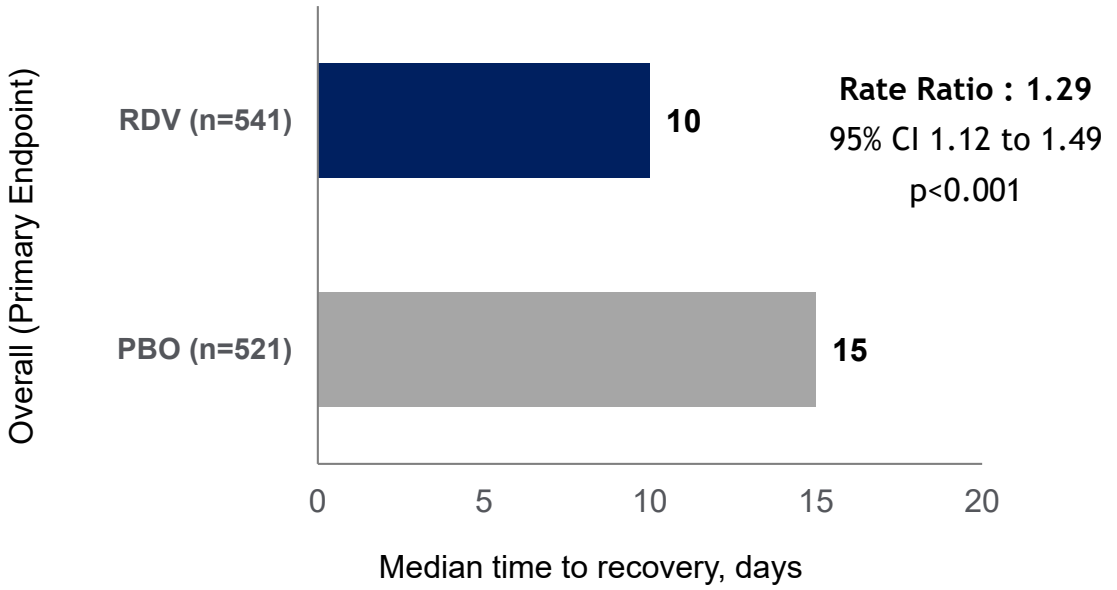
- There are additional ongoing studies evaluating safety and efficacy of RDV in various populations

*1.Beigel JH et al. NEJM 22 May 2020; 2. Wang Y et al. Lancet Apr 29 2020; 3.Goldman J et al. NEJM 27 May 2020; 4. Spinner CD et al. JAMA*

# 1 Shorter Time to Recovery and Discharge

## ACTT-1 (Patients across clinical spectrum)[1,2]

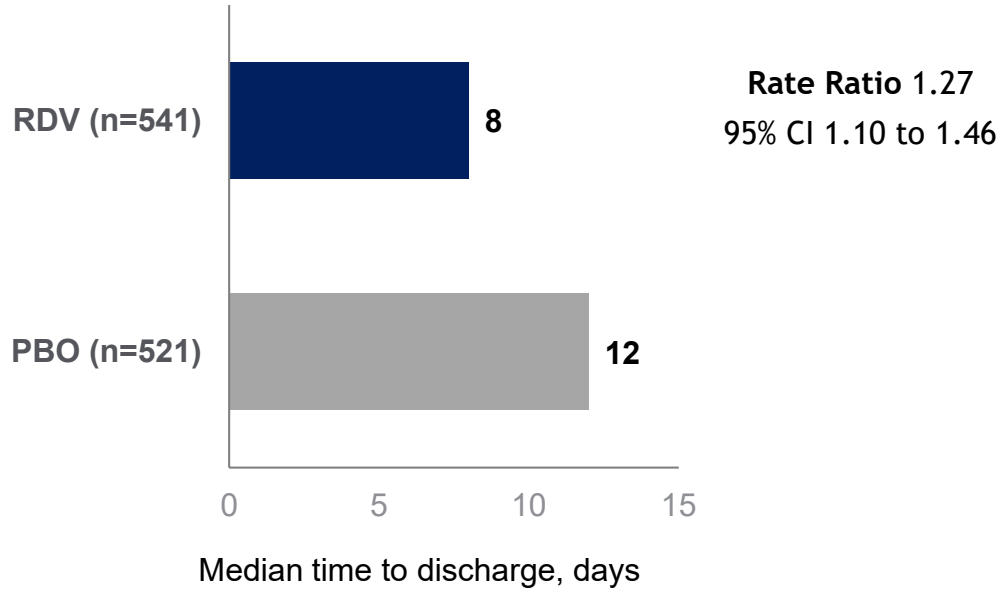
### Primary Endpoint: Time to Recovery




- Shorter time to recovery from 15 days to 10 days
- Larger benefits were observed in patients with severe disease

## ACTT-1 (Patients across clinical spectrum)[1,2]

### Time to Discharge or NEWS < 2 for 24 hours



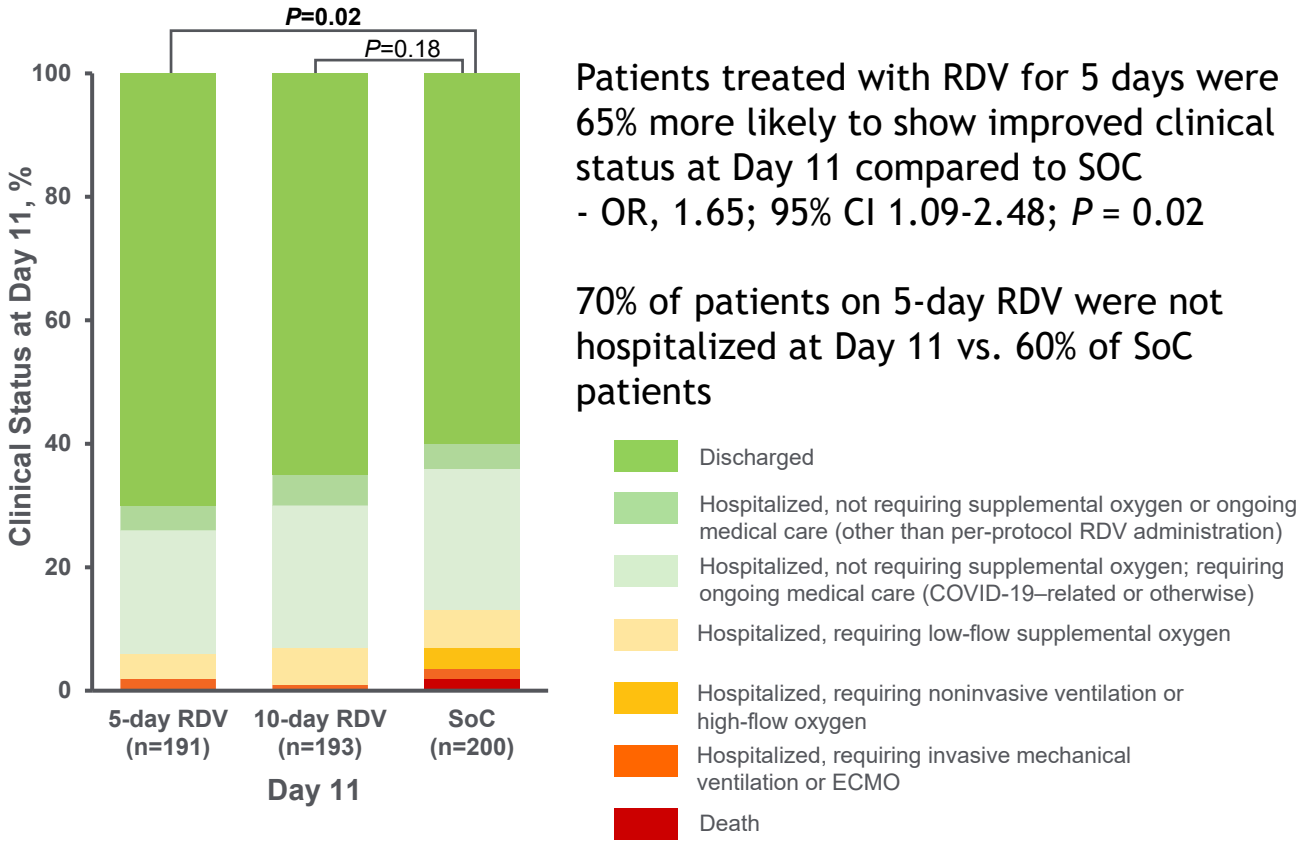

- Faster time to discharge or NEWS < 2 for 24 hours : 8 days vs 12 days compared to placebo
- Duration of hospitalization: 12 vs 17 days

*1. Beigel JH et al. NEJM 22 May 2020 ; 2.* https://clinicaltrials.gov/ct2/show/results/NCT04280705

# 2 Higher Rates of Clinical Improvement

## SIMPLE Moderate Trial

**Clinical Status at Day 11**

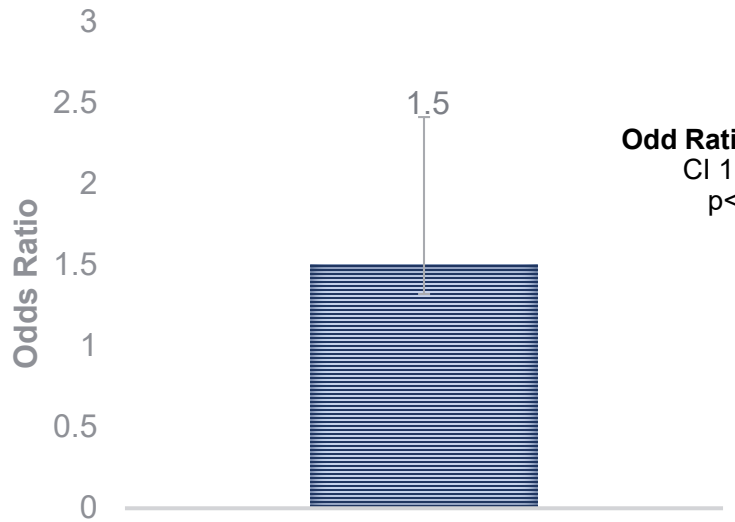



Patients treated with RDV for 5 days were 65% more likely to show improved clinical status at Day 11 compared to SOC
- OR, 1.65; 95% CI 1.09-2.48; *P* = 0.02

70% of patients on 5-day RDV were not hospitalized at Day 11 vs. 60% of SoC patients

## ACTT-1 (Patients across clinical spectrum)[2]

**Improvement at Day 15***




**Odd Ratio**: 1.50; 95% CI 1.2 to 1.9
p<0.001

**(N=1062)**

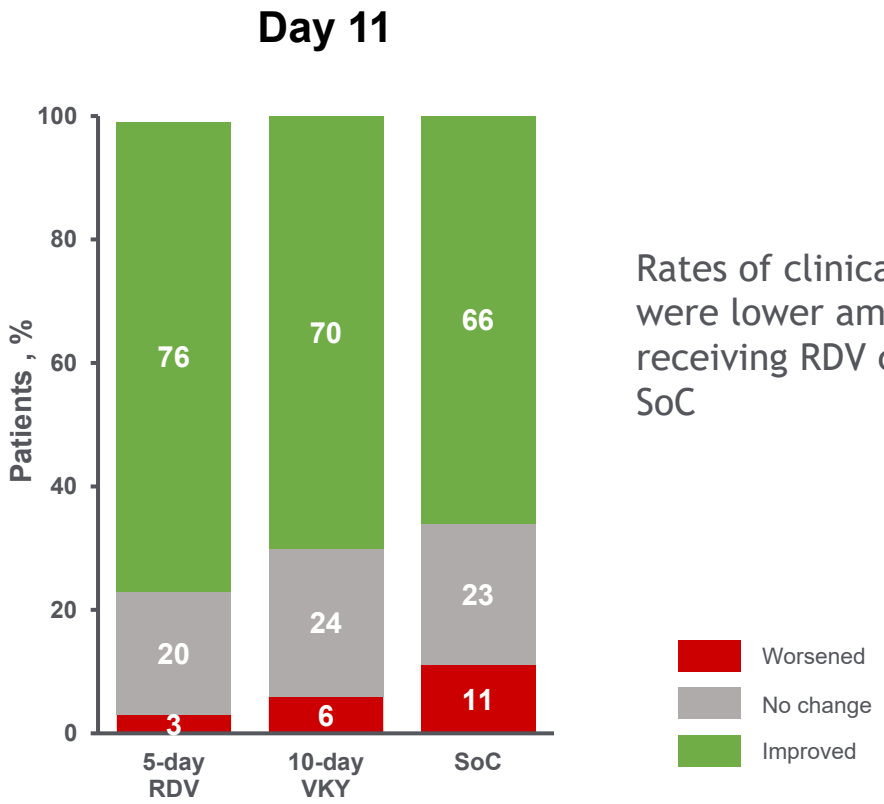
**Overall (Secondary Endpoint)**

- The odds of improvement in the ordinal scale score were 50% higher in the remdesivir group

*1. Spinner et al. JAMA 21 August 2020 ; 2. Beigel JH et al. NEJM 22 May 2020*

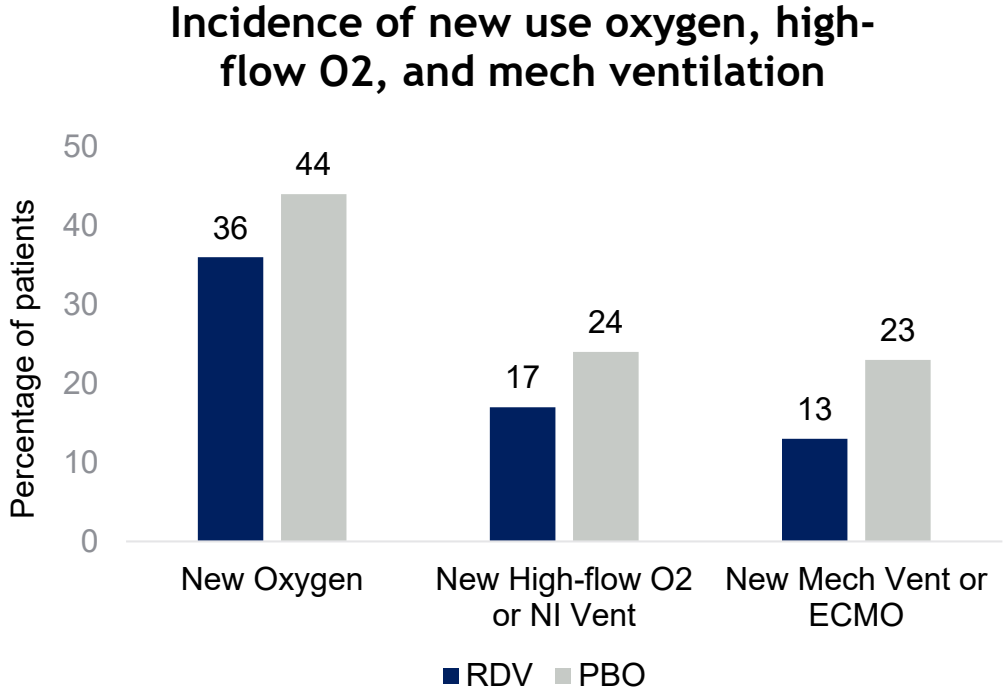
# 3 Decreased Disease Progression

## SIMPLE Moderate Trial [1]




Rates of clinical worsening were lower among patients receiving RDV compared to SoC

## ACTT-1 (Patients across clinical spectrum)[2,3]



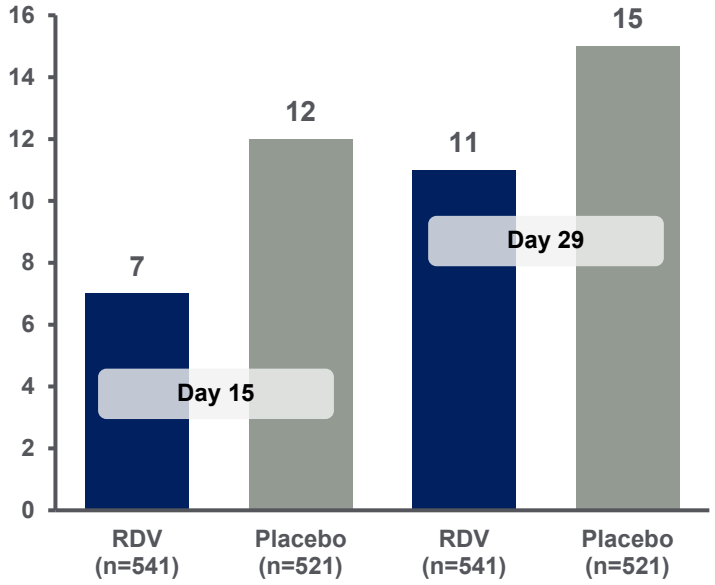

- Incidence of new use of oxygen, high-flow oxygen, mechanical ventilation or ECMO were all lower in patients treated with RDV

1. *Spinner et al. JAMA 21 August 2020 ; 2. Beigel JH et al. NEJM 22 May 2020; .3.* https://clinicaltrials.gov/ct2/show/NCT04280705

# 4 Mortality

## ACTT-1 (Overall Population)[1,2]

**Mortality by Day 15 and Day 29**




- Numerically lower mortality rates observed with RDV

***Mortality at Day 15 By Ordinal Score (preliminary data)***

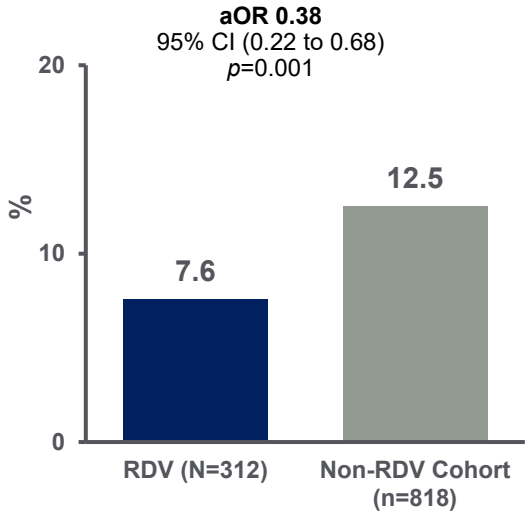
| | Hazard Ratio (95% CI) | Remdesivir vs Placebo Rates |
|---|---|---|
| Overall, N=1063 | 0.70 (0.47–1.04) | 7.1 vs 11.9 |
| No Oxygen (Ordinal 4), N = 138 | 0.46 (0.04–5.08) | 1.5 vs 2.5 |
| **Low flow Oxygen (Ordinal 5), N=435** | 0.22 (0.08–0.58) | **2.4 vs 10.9** |
| Hi-Flow $O_2$ or NIV (Ordinal 6), N=193 | 1.12 (0.53–2.38) | 15.2 vs 14.7 |
| Mechanical Ventilation (Ordinal 7), N= 285 | 1.06 (0.59–1.92) | 11.3 vs 14.1 |

- RDV was associated with a 72% significant reduction in mortality among patients requiring low-flow oxygen in a post-hoc analysis at day 14
- Similar results at day 29 per NIH treatment guidelines

## SIMPLE Severe vs. RWD (5807)[3]

**5-day or 10-day RDV versus SoC synthetic arm**

**Mortality at Day 14**




- RDV was associated with 62% reduction in mortality compared to a real-world SoC cohort by Day 14 in a retrospective study

1. Beigel JH et al. NEJM 22 May 2020, 2. https://clinicaltrials.gov/ct2/show/results/NCT04280705 ; 3. Olender SA et al. CID 24 July 2020

# Safety : SAEs Occuring in >1% by Treatment Group

| ACTT-1 (Overall Population)[1,2] | | | |
|---|---|---|---|
| **Organ Class** | **Serious AEs >1% in any arm** | **Remdesivir (N= 541) No (%)** | **Placebo (N=522) No (%)** |
| Any System Organ Class | Any | 131 (25) | 163 (32) |
| Renal and urinary | Acute kidney injury | 7 (1.3) | 12 (2.3) |
| | Renal failure | 2 (0.4) | 5 (1.0) |
| Respiratory, Thoracic and mediastinal disorders | Respiratory failure | 35 (6.6) | 58 (11.2) |
| | Acute respiratory failure | 8 (1.5) | 14 (2.7) |
| | Respiratory distress | 6 (1.1) | 11 (2.1) |
| | Acute respiratory distress syndrome | 7 (1.3) | 5 (1.0) |
| Infections and infestations | Septic shock | 8 (1.5) | 15 (2.9) |
| Vascular disorder | Hypotension | 4 (0.8) | 7 (1.4) |
| Cardiac disorders | Cardiac Arrest | 10 (1.9) | 7 (1.4) |

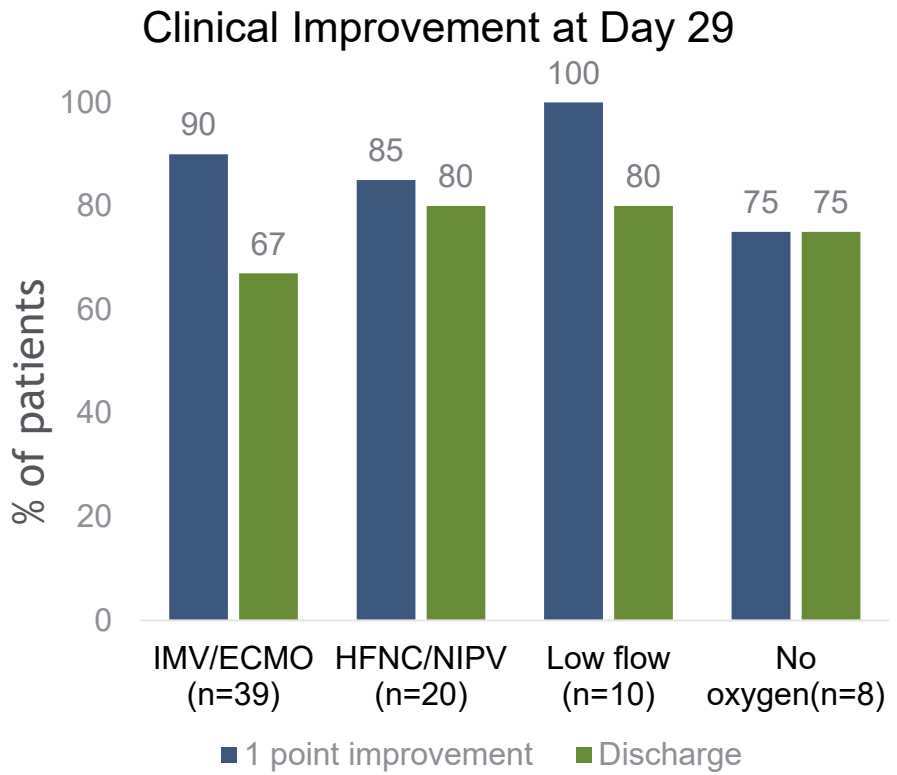
- Safety was similar in both groups
- Similar patterns observed in SIMPLE Moderate study suggesting that SAEs are driven primarily by underlying disease

*Beigel JH et al. NEJM 22 May 2020, .* https://clinicaltrials.gov/ct2/show/results/NCT04280705

# Compassionate Use of RDV in Vulnerable Populations

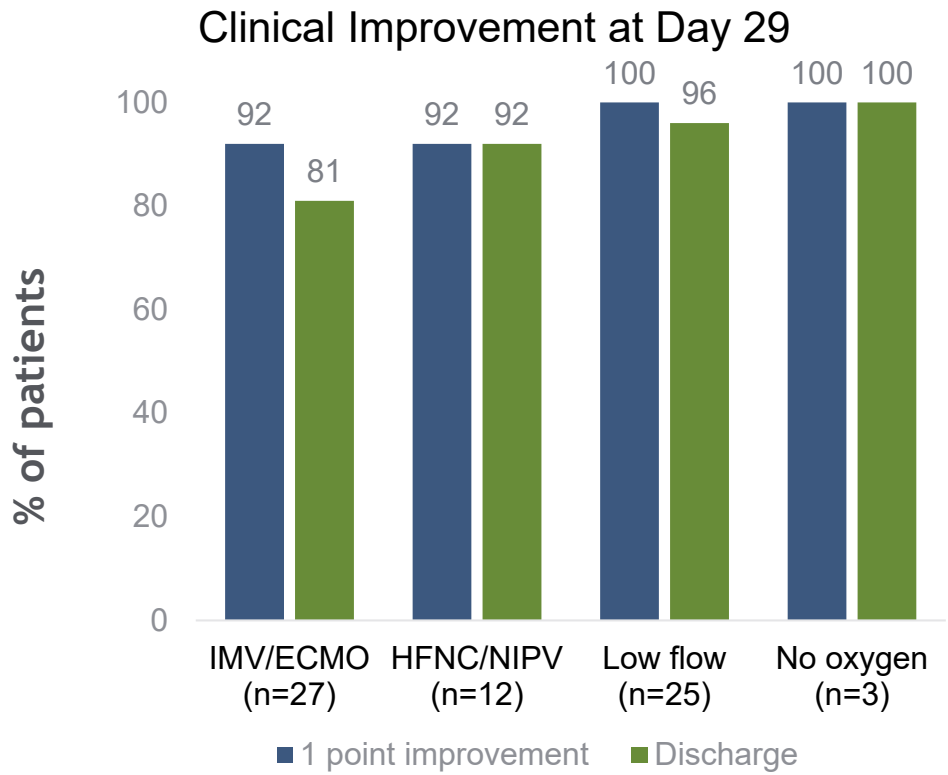
## Outcomes in 77 children

- *Age range : 1 month to 18 yrs; - 47% : < 12 yrs*
- *39 (53%) on IMV/ECMO at baseline*




## Outcomes in 67 pregnant women

- *Median Gestational age (weeks): 28 (14 -39)*
- *67% in the ICU, 40% on IMV/ECMO at baseline*






*Chiotos K, et al. IAS 2020. PE11763, Burwick R, et al. IAS 2020. PE11694*

# Remdesivir Combination Trials
## - Can combination therapies improve outcomes?

Remdesivir + Immunomodulators

- *JAK-1/2 inhibitor* *(Baricitinib, ACTT-2)*
- *IL-6 antibody* *(Tociluzimab, REMDACTA)*
- *IFN- Beta* *(IFN, ACTT-3)*
- *Bradykinin inhibtor* *(Icatibant, I-SPY)*
- *Anti-PDE4* *(Apremilast, I-SPY)*

Remdesivir + Neutralizing Antibodies

- *Monoclonal antibody* *(LY-CoV555, ACTIV3)*

Remdesivir + Convalescent Plasma

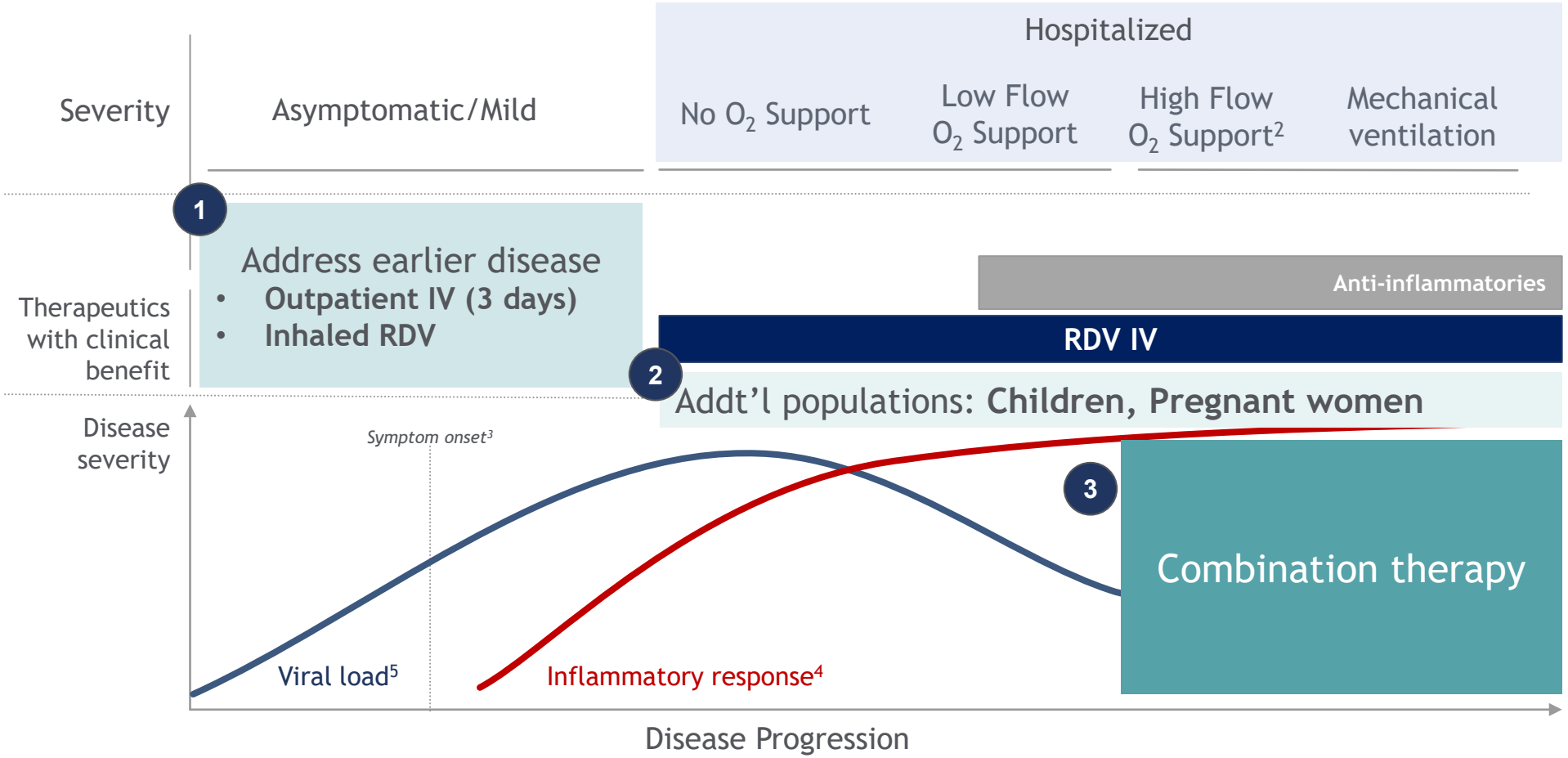
- *hIVIG* *(Plasma, INSIGHT Study)*

Remdesivir + Other Targets

- *Anti-CCR-5* *(Cenicriviroc, I-SPY)*
- *VE-PTP inhibitor* *(Razuprotafib, I-SPY)*
- *Antiviral* *(Merimepodib, Sponsored by ViralClear)*

https://clinicaltrials.gov/ct2/results?cond=Covid19&term=remdesivir&cntry=&state=&city=&dist=

# Remdesivir Next Steps




1. MMWR US (Jan22-May 30, 2020); 2. Hypothesis that most patients receiving High Flow $O_2$ support would be in the ICU (some may be in general wards); 3. Askur et al. Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in COVID-19. (2020). Allergy; 4. Zhou et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. (2020). Lancet 395; 5. Vardhana et al. The many faces of the anti-COVID immune response. (2020). *J. Exp. Med. 217*

# Acknowledgements


NIH NIAID

USAMRIID United States Army Medical Research Institute of Infectious Diseases Biodefense solutions to protect our nation

World Health Organization

CDC Centers for Disease Control and Prevention

UNC

COVANCE

Inserm

Vanderbilt University

Institut National de Recherche Biomédicale INRB Laboratoire National de Santé Publique

UAB

utmb Health Galveston National Laboratory

Médecins Sans Frontières Doctors Without Borders

Katholieke Universiteit Leuven Rega Instituut

University of Alberta

International Medical Corps

The Alliance for International Medical Action ALIMA

Protecting the Joint Force JPEO-CBRND Chemical, Biological, Radiological & Nuclear Defense

CDC 中国疾病预防控制中心 Chinese Center for Disease Control and Prevention

Capital Medical University CAPITAL MEDICAL UNIVERSITY