Remdesivir (GS-5734)

A Review of Pertinent Drug Information for SARS-CoV-2

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Remdesivir (GS-5734)

Mechanism of Action: Interference with viral RNA-dependent RNA polymerase; premature termination of viral RNA transcription

Status: Investigational, COVID-19 Phase III trials ongoing

Formulation: Intravenous only

Dosing: 200 mg IV loading dose, then 100 mg IV daily for 5-10 days
Pediatric Dosing: 5 mg/kg IV loading dose (max 200 mg), then 2.5 mg/kg IV daily (max 100 mg)

Manufacturer: Gilead Sciences

*Optimal duration currently under investigation
Monophosphoramidate 1’Cyano C-adenosine Nucleoside Analog
Monophosphoramidate 1’Cyano C-adenosine Nucleoside Analog
Remdesivir Structure Activity Relationship

C-Adenosine Analog

Monophosphate Form

Remdesivir

Siegel; ACS 2017.
C-Adenosine Analog
Rate limiting phosphorylation

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C-Adenosine Analog
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Monophosphate Form
Charge reduces permeability

Remdesivir

Siegel; ACS 2017.
C-Adenosine Analog
Rate limiting phosphorylation

Monophosphate Form
Charge reduces permeability

Remdesivir
Neutral charge, bypasses rate limiting step

Remdesivir Structure Activity Relationship

Siegel; ACS 2017.
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C-Adenosine Analog
Poor selectivity, highly cytotoxic

Remdesivir

Societ of Infectious Diseases Pharmacists

Siegel; ACS 2017.
Remdesivir Structure Activity Relationship

C-Adenosine Analog
Poor selectivity, highly cytotoxic

Remdesivir
1'Cyano modification confers selectivity

Siegel; ACS 2017.
Remdesivir (GS-5734) Pharmacokinetics

• **Distribution:** Unbound 12.1%; Widely distributed
  - Bladder, kidneys, liver, prostate gland, salivary gland (mandibular), pancreas
  - Seminal vesicle, epididymis, testes
  - Poorly crosses blood-brain barrier

• **Metabolism:** Phosphoramidate prodrug activated by esterases; CYP3A4 substrate

• **Elimination:** Renal 63%, biliary 27.8%

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Remdesivir (GS-5734)</th>
<th>Nucleoside Metabolite (GS-441524)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>$C_{\text{max}}$</strong></td>
<td>2.6 µg/mL</td>
<td>0.14-0.15 µg/mL</td>
</tr>
<tr>
<td><strong>$T_{\text{max}}$</strong></td>
<td>-</td>
<td>2.75-4 hr</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>0.84-1.04 hr</td>
<td>20.4-25.3 hr</td>
</tr>
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</table>
Safety

- Multiple-dose, 5-14 days
  - Any TEAE - 56-72%; All Grade 1-2
  - ALT/AST increase
    - Onset 5-25 days; resolution 3-47 days
- Phlebitis
- Constipation
- Dyspepsia
- Extremity pain
- Headache
- Nausea

- Ebola RCT
  - Single patient experienced hypotension and cardiac arrest after RDV initiation; cannot be distinguished from fulminant Ebola
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Sulfobutylether-beta Cyclodextrin (SBECO)
- Remdesivir 150 mg solution - 9 g
- Remdesivir 150 mg lyophylized powder - 4.5 g
- Voriconazole 400 mg - 6.4 g
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Does NOT meet NIOSH/ASHP criteria for hazardous compound

Consult updated pharmacy instructions from Gilead for additional information

**In vitro Activity**

**Filoviridae**
- Ebola
- Marburg

**Paramyxoviridae**
- Measles
- Mumps
- Nipah
- Hendra

**Pneumoviridae**
- Respiratory Syncytial Virus
- Human Metapneumovirus

**Orthocoronaviridae**
- HCoV-NL63
- HCoV-OC43
- HCoV-229E
- HCoV-HKU1
- MERS
- SARS-CoV-1
- SARS-CoV-2

HCoV = Human Coronavirus; MERS = Middle East Respiratory Syndrome; SARS = Severe Acute Respiratory Syndrome

<table>
<thead>
<tr>
<th>Virus</th>
<th>EC50 (cells)</th>
<th>CC50 (cells)</th>
<th>Selectivity Index</th>
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<tbody>
<tr>
<td>SARS-CoV-2</td>
<td>0.77 µM (Vero E6)</td>
<td>&gt;100 µM (Vero E6)</td>
<td>&gt;130</td>
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<tr>
<td>SARS-CoV-1</td>
<td>0.069 µM (HAE)</td>
<td>&gt; 10 µM (HAE)</td>
<td>&gt;144</td>
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<tr>
<td>MERS</td>
<td>0.074 µM (HAE)</td>
<td>&gt; 10 µM (HAE)</td>
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</tr>
<tr>
<td>Ebola</td>
<td>0.086 µM (Mcr)</td>
<td>6.1 (Hep-2)</td>
<td>N/A</td>
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EC50 = 50% effective concentration; CC50 = 50% cytotoxic concentration; Selectivity Index = CC50/EC50; Vero E6 = African monkey kidney cells; HAE = human airway epithelial cells; MCr = macrophages; Hep-2 = human epithelial type 2 cells.

Sheahan; Sci Transl Med 2017.  
Agostini; Am Soc Micro 2018.  
Yao; CID 2020.
### In vitro Activity

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- **SARS-CoV-2 EC50**
  - Ribavirin 109.5 µM
  - Penciclovir 95.96 µM
  - Favipiravir 61.9 µM
  - Hydroxychloroquine 0.77 µM
  - Chloroquine 1.13-5.47 µM

Sheahan; Sci Transl Med 2017.
Agostini; Am Soc Micro 2018.
Yao; CID 2020.
Coronaviruses and Proofreading

- Ribavirin
- Penciclovir
- Favipiravir
- Remdesivir

Removed by proofreading
Maintains activity; high fitness cost

References:
Agostini; mBio 2018.
Jordan; AAC 2018.
## In vivo Animal Prophylaxis

<table>
<thead>
<tr>
<th>Virus</th>
<th>Virologic</th>
<th>Clinical/Pathologic</th>
<th>Survival</th>
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<tr>
<td>SARS-CoV-1</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>MERS</td>
<td>✔</td>
<td>✔</td>
<td>✔️*</td>
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*MERS-infected mice showed improved survival; rhesus macaques euthanized day 6 post-infection unable to determine survival impact of remdesivir

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## In vivo Animal Treatment

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<tbody>
<tr>
<td>SARS-CoV1</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️ (Day 1)  ❌ (Day 2)</td>
</tr>
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<td>MERS</td>
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*MERS-infected mice did not show improved survival; rhesus macaques euthanized day 6 post-infection unable to determine survival impact of remdesivir; Macaques in Ebola model were euthanized if deemed clinically moribund

De wit E; Proc Natl Acad Sci 2020.  
Sheahan; Nat Comm 2020.  
Sheahan; Sci Transl Med 2017.  
“A drug that inhibits viral replication may be of little use once virus replication has reached its peak...”
Randomized, Controlled Ebola Trial

1:1:1:1
Stratified on cycle-threshold (i.e. viral load)
1o Outcome: 28 day mortality

- **Standard of Care +**
- **ZMapp (Control)**: Triple monoclonal antibody
- **Remdesivir (RDV)**: 200 mg load, 100 mg daily x9-13d
- **REGN-EB3**: Triple monoclonal antibody
- **MAb114**: Single Ebola survivor monoclonal

Mulangu; NEJM 2019.
- Similar duration of symptoms (~5.5 days)/viral load
  - Per day OR 1.12 (1.00-1.24)
- Baseline characteristics generally well matched
  - Higher SCr/LFTs in ZMapp/RDV (sicker?)
- ZMapp and RDV arms halted; mortality signal
Randomized, Controlled Ebola Trial

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Started too late? (latest start day 3)
Flaw in animal model?
Standard of care/resources?
First U.S. COVID-19 Case Report

35M, PMH (-) Cough/fever Travel from Wuhan

0

Urgent Care

4

SARS-CoV-2 (+) Admitted

5

SpO2 90% LLL opacity Abx started

10

O2 Stopped Rales resolve

12

Febrile

Cough

S streaky opacities/rales Supplemental O2 SARS-CoV-2 (+) RDV (evening)

11

Holshue; NEJM 2020.
Remdesivir in COVID-19

• Current data insufficient to draw conclusions
• Clinical trials and compassionate use ongoing

“[…] scientists are **patiently waiting** for the final results of these ongoing trials.”
Scientists patiently waiting for results
## Current Investigations

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sponsor</th>
<th>Population</th>
<th>Intervention</th>
<th>Renal</th>
<th>Completion*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adaptive</td>
<td>NIAID</td>
<td>n = 394</td>
<td>RDV vs. PCB; Adaptive</td>
<td>eGFR &lt; 30 mL/min</td>
<td>4/1/2023</td>
</tr>
<tr>
<td>Mild/Moderate</td>
<td>Gilead</td>
<td>SpO₂ ≥ 94%; n = 600</td>
<td>5 vs. 10 days RDV vs. SOC</td>
<td>CrCl &lt; 50 mL/min</td>
<td>5/2020</td>
</tr>
<tr>
<td>Severe*</td>
<td>Gilead</td>
<td>SpO₂ &lt; 94%; n = 400</td>
<td>5 vs. 10 days RDV vs. SOC</td>
<td>CrCl &lt; 50 mL/min</td>
<td>5/2020</td>
</tr>
<tr>
<td>Expanded</td>
<td>USAMR</td>
<td>U.S. DoD-Affiliates; All age</td>
<td>RDV</td>
<td>eGFR &lt; 30 mL/min</td>
<td>--</td>
</tr>
<tr>
<td>Mild/Mod (Ch)</td>
<td>CMU</td>
<td>SpO₂ &gt; 94%; n = 308</td>
<td>RDV vs. PCB</td>
<td>eGFR &lt; 30 mL/min</td>
<td>4/27/2020</td>
</tr>
<tr>
<td>Severe (Ch)</td>
<td>CMU</td>
<td>SpO₂ &lt; 94%; n = 453</td>
<td>RDV vs. PCB</td>
<td>eGFR &lt; 30 mL/min</td>
<td>5/1/2020</td>
</tr>
</tbody>
</table>

RDV = remdesivir; PCB = placebo; USAMR = U.S. Army Medical R&D Command; CMU = Capital Medical University, Beijing

*All data current as of 3/16/2020, subject to change

Source: ClinicalTrials.gov
Emergency Access

Gilead is transitioning the provision of emergency access to remdesivir from individual compassionate use requests to expanded access programs. This approach will both accelerate access to remdesivir for severely ill patients and enable the collection of data from all participating patients. These programs are currently under rapid development in conjunction with national regulatory authorities worldwide. More details on how to participate in the expanded access programs will be forthcoming.

During this transition period, we are unable to accept new individual compassionate use requests due to an overwhelming demand over the last several days. We are focused now on processing previously approved requests and anticipate the expanded access programs will initiate in a similar expected timeframe that any new requests for compassionate use would have been processed.

Exceptions will be made only for pregnant women or children less than 18 years of age with confirmed COVID-19 and severe manifestations of disease.

Given the importance of data generation, we urge you to enroll patients in clinical trials if reasonably possible rather than pursue an emergency treatment request. Please refer to the links below for information on current clinical trials investigating the use of remdesivir in COVID-19:

- NCT04280705
- NCT04292739
- NCT04292899
- 2020-000936-23

Thank you for your understanding as we work through this transition as rapidly as possible. We are grateful for all that you are doing to serve patients in your community as we work collectively to respond to this global health crisis.

Expanded Access Portal: https://rdvcu.gilead.com/
References

Questions

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