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; delayed chain 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
Remdesivir Structure Activity Relationship

C-Adenosine Analog

Monophosphate Form

Remdesivir

Siegel; ACS 2017.
Remdesivir Structure Activity Relationship

C-Adenosine Analog
Rate limiting phosphorylation

Monophosphate Form

Remdesivir

Siegel; ACS 2017.
Remdesivir Structure Activity Relationship

C-Adenosine Analog
Rate limiting phosphorylation

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

Siegel; ACS 2017.
Remdesivir Structure Activity Relationship

Monophosphoramidate 1’Cyano C-adenosine Nucleoside Analog

Siegel; ACS 2017.
Monophosphoramidate 1’Cyano C-adenosine Nucleoside Analog

Remdesivir Structure Activity Relationship

Siegel; ACS 2017.
Remdesivir Structure Activity Relationship

C-Adenosine Analog
Poor selectivity, highly cytotoxic

Remdesivir

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**: Phosphoramide 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>$C_{\text{max}}$</td>
<td>2.6 µg/mL</td>
<td>0.14-0.15 µg/mL</td>
</tr>
<tr>
<td>$T_{\text{max}}$</td>
<td>-</td>
<td>2.75-4 hr</td>
</tr>
<tr>
<td>Half-life</td>
<td>0.84-1.04 hr</td>
<td>20.4-25.3 hr</td>
</tr>
</tbody>
</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
Safety

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Sulfobutylether-beta Cyclodextrin (SBEC)

- Remdesivir 150 mg solution - 9 g
- Remdesivir 150 mg lyophylized powder - 4.5 g
- Voriconazole 400 mg - 6.4 g
Safety

• Multiple-dose, 5-14 days
  • Any TEAE - 56-72%; All Grade 1-2
  • ALT/AST increase
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Sulfobutylether-beta Cyclodextrin (SBEC)(D)

Remdesivir 150 mg solution - 9 g
Remdesivir 150 mg lyophylized powder - 4.5 g
Voriconazole 400 mg - 6.4 g

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

## In vitro Activity

<table>
<thead>
<tr>
<th>Virus</th>
<th>EC50 (cells)</th>
<th>CC50 (cells)</th>
<th>Selectivity Index</th>
</tr>
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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>
</tr>
<tr>
<td>SARS-CoV-1</td>
<td>0.069 µM (HAE)</td>
<td>&gt; 10 µM (HAE)</td>
<td>&gt;144</td>
</tr>
<tr>
<td>MERS</td>
<td>0.074 µM (HAE)</td>
<td>&gt; 10 µM (HAE)</td>
<td>&gt;135</td>
</tr>
<tr>
<td>Ebola</td>
<td>0.086 µM (Mcr)</td>
<td>6.1 (Hep-2)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

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.
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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

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

<table>
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<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>
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<tr>
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<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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<td>SARS-CoV1</td>
<td>✓</td>
<td>✓</td>
<td>✓ (Day 1)✓ (Day 2)</td>
</tr>
<tr>
<td>MERS</td>
<td>✓</td>
<td>✓</td>
<td>✗*</td>
</tr>
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<td>Ebola</td>
<td>✓</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

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
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• ZMapp and RDV arms halted; mortality signal

Started too late? (latest start day 3)
Flaw in animal model?
Standard of care/resources?
Compassionate Use Case Series

61 Patients
- 8 Excluded:
  - 7 No post-baseline data
  - 1 Erroneous start date

53 Patients
- 10 days: n = 40; 75%
- 5-9 days: n = 10; 19%
- < 5 days: n = 3; 6%

Median follow-up 18 days (IQR 13-23)
Compassionate Use Case Series

61 Patients

8 Excluded: 7 No post-baseline data 1 Erroneous start date

53 Patients

10 days: n = 40; 75%

5-9 days: n = 10; 19%

< 5 days: n = 3; 6%

### Characteristic

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<th>Characteristic</th>
<th>Patients (n = 53)</th>
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</thead>
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<tr>
<td>Median age (IQR) – yr</td>
<td>64 (48-71)</td>
</tr>
<tr>
<td>Male sex – no. (%)</td>
<td>40 (75)</td>
</tr>
<tr>
<td>Invasive ventilation – no. (%)</td>
<td>34 (64)</td>
</tr>
<tr>
<td>ECMO – no. (%)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Median Sx before RDV (IQR) – days</td>
<td>12 (9-15)</td>
</tr>
<tr>
<td>Coexisting conditions* – no. (%)</td>
<td>36 (68)</td>
</tr>
</tbody>
</table>

*Specific conditions – n (%): hypertension 13 (25), diabetes 9 (17), hyperlipidemia 6 (11), asthma 6 (11); ECMO = extracorporeal membrane oxygenation; Sx = symptoms; RDV = remdesivir

Grein; NEJM 2020.
**Compassionate Use Case Series**

No pre-specified endpoints

1 - Discharged
2 – Ambient air
3 – Low-flow
4 – High-flow/NIPPV
5 – MV/ECMO
6 – Death

MV = mechanical ventilation; NIPPV = non-invasive positive pressure ventilation
Compassionate Use Case Series

No pre-specified endpoints

1 - Discharged
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3 – Low-flow
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6 – Death

Mortality
N= 7/53 (13%)
Mean age 74.5 (range 68-79)

Improvement/Discharge
N= 36/53 (67.9%)

Worsening
N= 8/53 (15.1%)

MV = mechanical ventilation; NIPPV = non-invasive positive pressure ventilation

Grein; NEJM 2020.
Compassionate Use Case Series

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Improvement/Discharge
N= 36/53 (67.9%)

Worsening
N= 8/53 (15.1%)

Mortality
N= 7/53 (13%)
Mean age 74.5 (range 68-79)

28-day/discharge/death data unavailable
N= 17/53 (32.1%)
8 MV, 1 ECMO at last time-point
### Compassionate Use Case Series

<table>
<thead>
<tr>
<th>Adverse Events*</th>
<th>Patients – n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>32 (60)</td>
</tr>
<tr>
<td><strong>ALT/AST increase</strong></td>
<td><strong>12 (23)</strong></td>
</tr>
<tr>
<td>Renal impairment/AKI</td>
<td>7 (14)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Rash</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Hypernatremia</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Multi-organ dysfunction syndrome</td>
<td>3 (6)</td>
</tr>
</tbody>
</table>

Four patients discontinued for the following:

1. Worsening renal function
2. Multi-organ dysfunction
3. Transaminitis/rash
4. Transaminitis

“No new safety signals were detected in this compassionate use cohort of short-term remdesivir therapy.”

*Adverse events listed with >5% patients
Compassionate Use Case Series

Take home points:

• Difficult to interpret without control group
  • Natural course vs. remdesivir effects
  • Historical comparisons of limited value
  • No pre-specified endpoints
  • Median start day 12 of illness; no quantitative PCR to evaluate viral load progression

• High risk of bias
  • Selection – patients screened for compassionate use
  • Sampling – unclear if consecutive patients, not all compassionate use patients included
  • Reporting – 8 patients excluded for erroneous/lack of data, high proportion without endpoints

• Safety profile consistent with previous data
  • Toxicity vs. underlying disease
Severe RCT in China

Target Enrollment n=453 Terminated Early

255 Patients

18 Excluded
14 Ineligible
4 Withdrew

236 Patients

Placebo n = 78
Remdesivir n = 158

No dose: n = 3; 1.8%
< 5 days: n = 5; 3.2%
PP: n = 150; 94.9%

PP = Per protocol

Wang; Lancet 2020.
Severe RCT in China

### Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (n = 236)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (IQR) – yr</td>
<td>65 (56-71)</td>
</tr>
<tr>
<td>Male sex – no. (%)</td>
<td>140 (59.3)</td>
</tr>
<tr>
<td>Low-flow O₂ – no. (%)</td>
<td>129 (82)</td>
</tr>
<tr>
<td>HFNC/MV/ECMO – no. (%)</td>
<td>28 (18)</td>
</tr>
<tr>
<td>NEWS-2 – (IQR)</td>
<td>5 (3-7)</td>
</tr>
<tr>
<td>Median Sx (IQR) – days</td>
<td>10 (9-12)</td>
</tr>
<tr>
<td>Coexisting conditions* – no. (%)</td>
<td>167 (70.7)</td>
</tr>
<tr>
<td>Corticosteroids – no. (%)</td>
<td>91 (38.6)</td>
</tr>
</tbody>
</table>

**Placebo n = 78**  
**Remdesivir n = 158**

HFNC = high-flow nasal cannula; MV = mechanical ventilation; Sx = symptoms, NEWS-2 = National Early Warning Score-2  
*Most common = HTN (43.4%), diabetes (23.7%), coronary heart disease (7.2%)  
Concomitant antivirals permitted – LPV/r (17.8%), IFN-a2b (18.7%)

*Wang; Lancet 2020.*
Severe RCT in China

Improvement = 2-pt Reduction

1 - Discharged
2 - Ambient air
3 - Low-flow
4 - High-flow/NIPPV
5 - MV/ECMO
6 - Death

MV = mechanical ventilation; NIPPV = non-invasive positive pressure ventilation

Time to Improvement

21 d (IQR 13-28) vs. 23 d (15-28)
HR 1.23 (95%CI 0.87-1.75)

Hazard ratio 1.23 (95% CI 0.87-1.75); log-rank p=0.24
Severe RCT in China

Improvement = 2-pt Reduction

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Time to Improvement
21 d (IQR 13-28) vs. 23 d (15-28)
HR 1.23 (95%CI 0.87-1.75)

Improvement – Early (<10 day)
18 d (IQR 12-28) vs. 23 d (15-28)
HR 1.52 (95%CI 0.95-2.43)

28-Day Mortality
14% vs. 13%
Difference 1.1% (95%CI -8.1 to 10.3)

Wang; Lancet 2020.
Severe RCT in China

Deterioration

Figure S4. Kaplan Meier of time-to-clinical deterioration (defined as one category increase or death) in the intention-to-treat population.

Viral Load

SIDP
SOCIETY OF INFECTIOUS DISEASES PHARMACISTS
Wang; Lancet 2020.
Severe RCT in China

Placebo-controlled data

“Our study found that remdesivir was adequately tolerated and no new safety concerns were identified.”

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Remdesivir – n (%)</th>
<th>Placebo – n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>102 (66)</td>
<td>50 (64)</td>
</tr>
<tr>
<td>AST elevation</td>
<td>7 (5)</td>
<td>9 (12)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>16 (10)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Rash</td>
<td>11 (7)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Constipation</td>
<td>21 (14)</td>
<td>12 (15)</td>
</tr>
<tr>
<td>Serious</td>
<td>28 (18)</td>
<td>20 (26)</td>
</tr>
<tr>
<td>Acute Kidney Injury</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Requiring Discontinue</td>
<td>18 (12)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>ALT elevation</td>
<td>2 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>ARDS/resp. failure</td>
<td>7 (5)</td>
<td>1 (1)</td>
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Wang; Lancet 2020.
Severe RCT in China

Take home points:
• Control group!
  • Highest quality data to date
• Negative study
  • Underpowered – Remdesivir did not significantly reduce TTCR
  • Signal of larger reduction with early therapy (< 10-day) – interpret with caution
  • No difference in prevention of deterioration or mortality
• Safety
  • Well tolerated compared to control, low level of discontinuation

Wang; Lancet 2020.
Adaptive COVID Treatment Trial (ACTT-1)

*Preliminary Report

1107 Assessed

1063 Randomized

44 Excluded
25 Ineligible
19 Not enrolled

Placebo n = 522

Remdesivir n = 541

No dose: n = 4; 0.7%
Completed: n = 340; 65.3%

521 Analyzed

No dose: n = 10; 1.8%
Completed: n = 391; 72.6%

538 Analyzed

Completed: n = 391; 72.6%

Beigel; NEJM 2020.
## Adaptive COVID Treatment Trial (ACTT-1)

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<tr>
<th>Characteristic</th>
<th>Remdesivir (n = 541)</th>
<th>Placebo (n = 522)</th>
</tr>
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<tbody>
<tr>
<td>Median age (IQR) – yr</td>
<td>58.6 (14.6)</td>
<td>59.2 (15.4)</td>
</tr>
<tr>
<td>Male sex – no. (%)</td>
<td>352 (65.1)</td>
<td>332 (63.6)</td>
</tr>
<tr>
<td>Median Sx (IQR) – days</td>
<td>9 (6-12)</td>
<td>9 (7-13)</td>
</tr>
<tr>
<td>Comorbidities ≥ 2* – no. (%)</td>
<td>245 (52.5)</td>
<td>234 (51.7)</td>
</tr>
<tr>
<td>Baseline Status – no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline – 4 (Ambient Air)</td>
<td>67 (12.4)</td>
<td>60 (11.5)</td>
</tr>
<tr>
<td>Baseline – 5 (Low-flow)</td>
<td>222 (41.0)</td>
<td>199 (38.1)</td>
</tr>
<tr>
<td>Baseline – 6 (High-flow)</td>
<td>98 (18.1)</td>
<td>99 (19.0)</td>
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<tr>
<td>Baseline – 7 (MV/ECMO)</td>
<td>125 (23.1)</td>
<td>147 (28.2)</td>
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MV = mechanical ventilation; Sx = symptoms, *Most common = HTN (49.6%), obesity (37.0%), diabetes (29.7%)
Adaptive COVID Treatment Trial (ACTT-1)

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Time to Recovery = Status 1-3

1 – Discharged
2 – Discharged; Limits
3 – Inpatient; No care
4 – Ambient Air
5 – Low-flow
6 – High-flow/NIPPV
7 – MV/ECMO
8 – Death

MV = mechanical ventilation; Sx = symptoms, *Most common = HTN (49.6%), obesity (37.0%), diabetes (29.7%)
Adaptive COVID Treatment Trial (ACTT-1)

Time to Recovery
- Remdesivir 11 d vs. Placebo 15 d
  - RR 1.32 (95%CI 1.12-1.55; P<0.001)

Adjusted for baseline clinical status
- RR 1.31 (95%CI 1.12-1.57)
Adaptive COVID Treatment Trial (ACTT-1)

Time to Recovery

Remdesivir 11 d vs. Placebo 15 d
RR 1.32 (95%CI 1.12-1.55; P<0.001)

*Confidence intervals unadjusted for multiplicity; Should not be used to infer treatment effects
Adaptive COVID Treatment Trial (ACTT-1)

“A test of interaction of treatment with baseline score on the ordinal scale was not significant.”
Adaptive COVID Treatment Trial (ACTT-1)

Day 15 Clinical Worsening – Remdesivir vs. Placebo

Ambient Air
8.3% vs. 15.7%

Low-flow
8.7% vs. 21.8%

High-flow
25.4% vs. 33.7%

MV/ECMO
13.9% vs. 16.5%
Adaptive COVID Treatment Trial (ACTT-1)

Day 15 – Clinical Status*
OR 1.50 (95%CI 1.18 to 1.91)

*Original primary endpoint

Figure S5. Histogram of ordinal scores at Day 15 by treatment arm

Proportion

Recovery

Death

Placebo
Remdesivir
Adaptive COVID Treatment Trial (ACTT-1)

Day 15 – Clinical Status
OR 1.50 (95%CI 1.18 to 1.91)

Mortality
KM Estimate 7.1% vs. 11.9%
HR 0.70 (95%CI 0.47-1.04)

KM = Kaplan-Meier
Adaptive COVID Treatment Trial (ACTT-1)

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Remdesivir (n = 541)</th>
<th>Placebo (n = 522)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serious – n (%)</strong></td>
<td>114 (21.1)</td>
<td>141 (27)</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>7 (1.3)</td>
<td>9 (1.7)</td>
</tr>
<tr>
<td>Hypoxia/resp. failure</td>
<td>13 (2.4)</td>
<td>15 (2.9)</td>
</tr>
<tr>
<td>Hypotension/shock</td>
<td>6 (1.1)</td>
<td>15 (2.9)</td>
</tr>
<tr>
<td><strong>Any</strong></td>
<td>156 (28.8)</td>
<td>172 (33.0)</td>
</tr>
<tr>
<td>Anemia/Hgb decrease</td>
<td>43 (7.9)</td>
<td>47 (9.0)</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>40 (7.4)</td>
<td>38 (7.3)</td>
</tr>
<tr>
<td>AST/ALT elevation</td>
<td>22 (4.1)</td>
<td>31 (5.9)</td>
</tr>
<tr>
<td>Lymphocyte decrease</td>
<td>13 (2.4)</td>
<td>18 (3.4)</td>
</tr>
</tbody>
</table>

Generally well tolerated overall

Higher rates of adverse events in placebo arm than remdesivir; High morbidity of disease

Hgb = hemoglobin

Beigel; NEJM 2020.
Adaptive COVID Treatment Trial (ACTT-1)

Take home points:

• **Significant reduction in time to recovery**
  - Similar benefit in baseline-adjusted analysis
  - Most prominently demonstrated in baseline category 5; largest group vs. most benefit?
  - No apparent benefit observed in MV/ECMO at baseline; follow-up time inadequate?
  - Benefit observed in subgroup > 10 days since symptom onset

• **Mortality**
  - No statistically significant reduction in mortality; Arguably clinically significant reduction

• **Preliminary Results**
  - 301 patients continuing trial/not recovered

• **Safety**
  - Lower adverse event rate compared to placebo group; well-tolerated

Beigel; NEJM 2020.
SIMPLE-1 Severe – 5 vs. 10 days

- 408 Screened
  - 397 Started
    - 5 Ineligible
      - 1 Discharged
      - 5 No treatment
    - Excluded MV/ECMO MODS

- 5-Day n = 200
- 10-Day n = 197

MODS = multi-organ dysfunction syndrome

Goldman; NEJM 2020.
408 Screened

5 Ineligible
1 Discharged
5 No treatment

397 Started

5-Day n = 200

10-Day n = 197

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>5 Day (n = 200)</th>
<th>10 Day (n = 197)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (IQR) – yr</td>
<td>58.6 (14.6)</td>
<td>59.2 (15.4)</td>
</tr>
<tr>
<td>Male sex – no. (%)</td>
<td>120 (60)</td>
<td>133 (68)</td>
</tr>
<tr>
<td>Median Sx (IQR) – days</td>
<td>8 (5-11)</td>
<td>9 (6-12)</td>
</tr>
<tr>
<td>Hosp. days before RDV (IQR)</td>
<td>2 (1-3)</td>
<td>2 (1-3)</td>
</tr>
<tr>
<td><strong>Baseline Status – no. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline – Ambient Air</td>
<td>34 (17)</td>
<td>21 (11)</td>
</tr>
<tr>
<td>Baseline – Low-flow</td>
<td>113 (56)</td>
<td>107 (54)</td>
</tr>
<tr>
<td>Baseline – High-flow</td>
<td>49 (24)</td>
<td>60 (30)</td>
</tr>
<tr>
<td>Baseline – MV/ECMO</td>
<td>4 (2)</td>
<td>9 (5)</td>
</tr>
</tbody>
</table>

&P=0.02 for comparison via Wilcoxon rank-sum test

Goldman; NEJM 2020.
SIMPLE-1 Severe – 5 vs. 10 days

14 Day Clinical Status

- 7 - Discharged
- 6 – Ambient air; no care
- 5 – Ambient air; care
- 4 – Low-flow
- 3 – High-flow/NIV
- 2 – MV/ECMO
- 1 – Death

MV = mechanical ventilation; NIV= non-invasive ventilation

P=0.14
Stratified Wilcoxon rank-sum

Adjusted for baseline clinical status

Goldman; NEJM 2020.
SIMPLE-1 Severe – 5 vs. 10 days

7 - Discharged
6 – Ambient air; no care
5 – Ambient air; care
4 – Low-flow
3 – High-flow/NIV
2 – MV/ECMO
1 – Death

14 Day Clinical Status
P=0.14
Stratified Wilcoxon rank-sum

Time to Improvement (2-pt)
10 d vs. 11 d
Adj. HR 0.79 (95%CI 0.61-1.01)

Time to Recovery (Score 6 or 7)
10 d vs. 11 d
Adj. HR 0.81 (95%CI 0.64-1.04)

MV = mechanical ventilation; NIV= non-invasive ventilation
SIMPLE-1 Severe – 5 vs. 10 days

Caution:
- Post-hoc analysis
- Small subgroups
- Inconsistent trends
# SIMPLE-1 Severe – 5 vs. 10 days

## Day 14 Improvement

<table>
<thead>
<tr>
<th>No. of Patients in Oxygen-Support Group at Day 14 (%)</th>
<th>5-day course of remdesivir (N=193)*</th>
<th>10-day course of remdesivir (N=188)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive</td>
<td>1 (25)</td>
<td>4 (50)</td>
</tr>
<tr>
<td>Noninvasive</td>
<td>8 (16)</td>
<td>13 (22)</td>
</tr>
<tr>
<td>Low-flow oxygen</td>
<td>5 (5)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Ambient air</td>
<td>2 (6)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Non-invasive</td>
<td>2 (50)</td>
<td></td>
</tr>
<tr>
<td>Invasive</td>
<td>6 (12)</td>
<td>19 (33)</td>
</tr>
<tr>
<td>Noninvasive</td>
<td>8 (7)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Low-flow oxygen</td>
<td>0</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Ambient air</td>
<td>3 (38)</td>
<td></td>
</tr>
<tr>
<td>Discharged</td>
<td>1 (25)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Non-invasive</td>
<td>7 (14)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Low-flow oxygen</td>
<td>2 (2)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Ambient air</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Improvement</td>
<td>1 (25)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Non-invasive</td>
<td>28 (57)</td>
<td>82 (80)</td>
</tr>
<tr>
<td>Low-flow oxygen</td>
<td>84 (79)</td>
<td>13 (65)</td>
</tr>
</tbody>
</table>

**Improvement: ACTT-1 Placebo**

<table>
<thead>
<tr>
<th></th>
<th>44.3%</th>
<th>58.5%</th>
<th>74.5%</th>
<th>76.6%</th>
<th>44.3%</th>
<th>58.5%</th>
<th>74.5%</th>
<th>76.6%</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIDP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Goldman; NEJM 2020.
SIMPLE-1 Severe – 5 vs. 10 days

Take home points:
• No significant difference between 5 vs. 10 days
  • Analysis adjusted for baseline clinical status
  • Important implications given limited supply
• MV/ECMO at day 5 receiving additional 5 days had lower mortality
  • Post-hoc analysis, small subgroups ≠ causal
  • Inconsistent trends (high-flow 10 day worse than 5 day)

Goldman; NEJM 2020.
## Available Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lancet Severe RCT</th>
<th>ACTT-1</th>
<th>SIMPLE Severe</th>
<th>SIMPLE Moderate &amp;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample, (n)</td>
<td>237</td>
<td>1063</td>
<td>397</td>
<td>584</td>
</tr>
<tr>
<td>Severity</td>
<td>Hypoxia/PNA/PF &lt; 300</td>
<td>Hypoxia/PNA/Supp. O2</td>
<td>PNA/Hypoxia; Not MV</td>
<td>SpO₂ ≥ 94%</td>
</tr>
<tr>
<td>Sx duration, days (IQR)</td>
<td>10 (9-12)</td>
<td>9 (6-12)</td>
<td>9 (7-13)</td>
<td>--</td>
</tr>
<tr>
<td>Intervention</td>
<td>10-day PBO</td>
<td>10-day PBO</td>
<td>5-day</td>
<td>10-day SOC</td>
</tr>
<tr>
<td>Mortality (28d), (%)</td>
<td>14</td>
<td>13</td>
<td>8</td>
<td>11.6</td>
</tr>
<tr>
<td>TTCR (days)/Recovery (%)</td>
<td>21 days</td>
<td>23 days</td>
<td>11 days*</td>
<td>15 days*</td>
</tr>
<tr>
<td>AEs Discontinue Tx, n (%)</td>
<td>18 (12)</td>
<td>4 (5)</td>
<td>36 (6.7)</td>
<td>36 (6.9)</td>
</tr>
</tbody>
</table>

Sx = symptoms; TTCR = time to clinical recovery; AE = adverse effects; Tx = treatment

&Preliminary results

*p<0.001

**14-day mortality data

+11-day mortality data

Wang; Lancet 2020.
Beigel; NEJM 2020.
Goldman; NEJM 2020.

Clinical Summary

- Remdesivir significantly reduces time to clinical recovery
  - Benefit most apparent in baseline low-flow patients
  - Minimal/no benefit observed in ≥ high-flow; Longer follow-up data needed
- Clinically, but not statistically significant mortality reduction in ACTT-1
- Data not supportive of 10-day symptom cutoff
- In patients who derive benefit, 5-days = 10-days
- Serious and non-serious adverse events similar/lower than placebo
  - Well-tolerated overall
### Current Investigations

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sponsor</th>
<th>Population</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTT-2</td>
<td>NIAID</td>
<td>SpO$_2 &lt; 94%$</td>
<td>RDV ± baracitinib; Adaptive</td>
</tr>
<tr>
<td>SIMPLE-2 Mod</td>
<td>Gilead</td>
<td>SpO$_2 ≥ 94%$</td>
<td>5 vs. 10 days RDV vs. SOC; Extension</td>
</tr>
<tr>
<td>DisCoVeRy</td>
<td>Inserm</td>
<td>SpO$_2 &lt; 94%$</td>
<td>RDV vs. HCQ vs. IFN-ß vs. LPV/r vs. SOC</td>
</tr>
<tr>
<td>Solidarity</td>
<td>WHO</td>
<td>Hospitalized</td>
<td>RDV vs. HCQ vs. LPV/r vs. IFN-ß1a</td>
</tr>
</tbody>
</table>

RDV = remdesivir; PCB = placebo; HCQ = hydroxychloroquine; LPV/r = lopinavir/ritonavir; IFN-ß = interferon beta; *Estimated completion; Current as of 4/15/2020, subject to change; Source: ClinicalTrials.gov


References

21. Chin-Hong, Peter (PCH_SF). We have fielded a lot of requests from around the country for our experience with getting #compassionateuse #remdesivir from #Gilead for critically ill #COVID19 pts. Pears:1)~72 hrs if approved 2)Many steps but doable 3)Model of #interprofessional ID/IDPharm aloha. We are all in.” 3/16/20:20:16. Tweet.
Updates Log

3/24/2020 – Original version posted
4/5/2020 – Community transmission case report; ongoing trial info updated
4/12/2020 – Compassionate use case series added; ongoing trial info updated
4/17/2020 – Updated trial info
4/29/2020 – Lancet Severe Trial, NIAID/SIMPLE prelim data, Updated trial info
5/1/2020 – Emergency Use Authorization
6/6/2020 – ACTT-1, SIMPLE-1, SIMPLE-2 top-line results, trials updated
Questions

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