Remdesivir (GS-5734)

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

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Remdesivir (GS-5734)

Mechanisms:
1. Interference RNA-dependent RNA polymerase → delayed termination of RNA transcription
2. Template incorporation inhibiting complementary base addition/replication

Status: FDA Approved 10/22/2020

Formulation: Intravenous only, inhalational formulation in early trials

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

DOI: 10.3390/v11040326, DOI: 10.1074/jbc.AC120.015720
Remdesivir Structure Activity Relationship

Monophosphoramidate 1’Cyano C-adenosine Nucleoside Analog

Siegel; ACS 2017. DOI: 10.1021/acs.jmedchem.6b01594
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. DOI: 10.1021/acs.jmedchem.6b01594
Remdesivir Structure Activity Relationship

Monophosphoramidate 1’Cyano C-adenosine Nucleoside Analog

Siegel; ACS 2017. DOI: 10.1021/acs.jmedchem.6b01594
Remdesivir Structure Activity Relationship

C-Adenosine Analog
Poor selectivity, highly cytotoxic

Remdesivir
1’Cyano modification confers selectivity

Siegel; ACS 2017. DOI: 10.1021/acs.jmedchem.6b01594
**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**: Predominantly in urine as GS-441524, partially in feces

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Remdesivir (GS-5734)</th>
<th>Nucleoside Metabolite (GS-441524)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>2.6 µg/mL</td>
<td>0.14-0.15 µg/mL</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt;</td>
<td>-</td>
<td>1.5-2 hr</td>
</tr>
<tr>
<td>Half-life</td>
<td>0.89-0.98 hr</td>
<td>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
• Extremity pain
• Constipation
• Dyspepsia
• Nausea
• Headache
Safety

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  • Any TEAE - 56-72%; All Grade 1-2
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Sulfobutylether-beta Cyclodextrin (SBECO)
- Remdesivir 100 mg solution - 6 g
- Remdesivir 100 mg lyophylized powder - 3 g
- Voriconazole 400 mg - 6.4 g

Minimal clinical significance

Adamsick; JASN 2020. DOI: 10.1681/ASN.2020050589
### In vitro Activity

<table>
<thead>
<tr>
<th>Filoviridae</th>
<th>Paramyxoviridae</th>
<th>Pneumoviridae</th>
<th>Orthocoronaviridae</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Ebola</td>
<td>● Measles</td>
<td>● Respiratory Syncytial Virus</td>
<td>● HCoV-NL63</td>
</tr>
<tr>
<td>● Marburg</td>
<td>● Mumps</td>
<td>● Human Metapneumovirus</td>
<td>● HCoV-OC43</td>
</tr>
<tr>
<td></td>
<td>● Nipah</td>
<td></td>
<td>● HCoV-229E</td>
</tr>
<tr>
<td></td>
<td>● Hendra</td>
<td></td>
<td>● HCoV-HKU1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>● MERS-CoV</td>
</tr>
<tr>
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<td>● SARS-CoV-1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>● SARS-CoV-2</td>
</tr>
</tbody>
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HCoV = Human Coronavirus; MERS = Middle East Respiratory Syndrome; SARS = Severe Acute Respiratory Syndrome

Lo; Sci Rep 2017. DOI: 10.1038/srep43395
Sheahan; Sci Transl Med 2017. DOI: 10.1126/scitranslmed.aal3653
In vitro Activity

Highly conserved nsp12 (RNA polymerase) across relevant coronaviruses

Broad activity against coronaviruses

Spike protein (viral cell entry) less conserved = host species diversity

Sheahan; Sci Transl Med 2017. DOI: 10.1126/scitranslmed.aal3653
# In vitro Activity

<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>0.01 µM (HAE)</td>
<td>&gt;100 µM (HAE)</td>
<td>&gt;1000</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>
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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>
</tr>
</tbody>
</table>

EC50 = 50% effective concentration; CC50 = 50% cytotoxic concentration; Selectivity Index = CC50/EC50; HAE = human airway epithelial cells; MCr = macrophages; Hep-2 = human epithelial type 2 cells

Pruijssers; Cell Reports 2020. DOI: 10.1016/j.celrep.2020.107940
Gordon; J Bio Chem 2020. DOI: 10.1074/jbc.AC120.013056
Sheahan; Sci Transl Med 2017. DOI: 10.1126/scitranslmed.aal3653
Agostini; Am Soc Micro 2018. DOI: 10.1128/mBio.00221-18
Yao; CID 2020. DOI: 10.1093/cid/ciaa237
## In vitro Activity

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**SARS-CoV-2 EC50**
- Ribavirin 109.5 µM
- Penciclovir 95.96 µM
- Favipiravir 61.9 µM

Pruijssers; Cell Reports 2020. DOI: 10.1016/j.celrep.2020.107940
Gordon; J Bio Chem 2020. DOI: 10.1074/jbc.AC120.013056
Sheahan; Sci Transl Med 2017. DOI: 10.1126/scitranslmed.aal3653
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**In vitro Activity**

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<tr>
<th>Analysis</th>
<th>Remdesivir</th>
<th>GS-441524</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell Line*</td>
<td>Vero E6</td>
<td>Calu3 2B4</td>
</tr>
<tr>
<td>EC$_{50}$ (µM)</td>
<td>1.65</td>
<td>0.28</td>
</tr>
<tr>
<td>24h RDV-TP (pmol/10$^6$ cells)</td>
<td>0.54 ± 0.15</td>
<td>2.17 ± 0.14</td>
</tr>
</tbody>
</table>

Cell lines: Vero E6 = African green monkey kidney cells; Calu3 2B4 = human lung cells; HAE = human airway epithelial cells; EC$_{50}$ measured via plaque assay technique; RDV-TP = Remdesivir tri-phosphate (pharmacologically active)

Pruijssers; Cell Reports 2020. DOI: 10.1016/j.celrep.2020.107940
Coronaviruses and Proofreading

Ribavirin

Penciclovir

Favipiravir

Remdesivir

Removed by proofreading

Maintains activity; high fitness cost

Agostini; Am Soc Micro 2018. DOI: 10.1128/mBio.00221-18
Smith; PLoS Pathog 2013. DOI: 10.1371/journal.ppat.1003565
Wang; Cell Res 2020. DOI: 10.1038/s41422-020-0282-0
Jordan; AAC 2018. DOI: 10.1177/2040206618764483.
Coronaviruses and Proofreading

Modest activity change w/o ExoN

![Graph A: Change in Viral Titer](image)

![Graph B: % Inhibition](image)

Agostini; Am Soc Micro 2018. DOI: 10.1128/mBio.00221-18
### In vivo Animal Prophylaxis

<table>
<thead>
<tr>
<th>Virus</th>
<th>Virologic</th>
<th>Clinical/Pathologic</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>SARS-CoV-1</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>MERS</td>
<td>✔</td>
<td>✔</td>
<td>✔*</td>
</tr>
</tbody>
</table>

*MERS-infected mice showed improved survival; rhesus macaques euthanized day 6 post-infection unable to determine survival impact of remdesivir

De Wit E; Proc Natl Acad Sci 2020. DOI: 10.1073/pnas.1922083117.
Sheahan; Nat Comm 2020. DOI: 10.1038/s41467-019-13940-6.
Sheahan; Sci Transl Med 2017. DOI: 10.1126/scitranslmed.aal3653.
### In vivo Animal Treatment

<table>
<thead>
<tr>
<th>Virus</th>
<th>Virologic</th>
<th>Clinical/Pathologic</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>SARS-CoV-1</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️ (Day 1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>✗ (Day 2)</td>
</tr>
<tr>
<td>MERS</td>
<td>✔️</td>
<td>✔️</td>
<td>*</td>
</tr>
<tr>
<td>Ebola</td>
<td>✔️</td>
<td>✔️</td>
<td>---</td>
</tr>
<tr>
<td>SARS-CoV-2&amp;</td>
<td>✔️</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

*Chimeric SARS-CoV strain expressing SARS-CoV2 RNA polymerase

De wit E; Proc Natl Acad Sci 2020. DOI: 10.1073/pnas.1922083117
Sheahan; Nat Comm 2020. DOI: 10.1038/s41467-019-13940-6
Sheahan; Sci Transl Med 2017. DOI: 10.1126/scitranslmed.aal3653
Warren; Nature 2016. DOI: 10.1038/nature17180
Pruijssers; Cell Reports 2020. DOI: 10.1016/j.celrep.2020.107940
Severe RCT in China

255 Patients

18 Excluded
14 Ineligible
4 Withdrawed

236 Patients

Target Enrollment
n=453
Terminated Early

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

Remdesivir n = 158

Wang; Lancet 2020. DOI: 10.1016/S0140-6736(20)31022-9
**Severe RCT in China**

<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>

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%)
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)

Wang; Lancet 2020. DOI: 10.1016/S0140-6736(20)31022-9
Severe RCT in China

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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. DOI: 10.1016/S0140-6736(20)31022-9
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

Wang; Lancet 2020. DOI: 10.1016/S0140-6736(20)31022-9
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. DOI: 10.1016/S0140-6736(20)31022-9
Severe RCT in China

Take home points:
• Placebo controlled, RCT
• 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. DOI: 10.1016/S0140-6736(20)31022-9
Adaptive COVID Treatment Trial (ACTT-1)

1114 Assessed
- 52 Excluded
  - 28 Ineligible
  - 24 Not enrolled

1062 Randomized
- Placebo n = 521
  - Full 10-day n = 226; 43.3%
  - No dose: n = 4; 0.7%
  - 521 Analyzed
- Remdesivir n = 541
  - Full 10-day n = 208; 38.4%
  - No dose: n = 10; 1.8%
  - 541 Analyzed

Beigel; NEJM 2020. DOI: 10.1056/NEJMoa2007764
### Adaptive COVID Treatment Trial (ACTT-1)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Remdesivir (n = 541)</th>
<th>Placebo (n = 522)</th>
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<tbody>
<tr>
<td>Mean age (SD) – 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>296 (55.7)</td>
<td>283 (54.7)</td>
</tr>
<tr>
<td><strong>Baseline Status – no. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline – 4 (Ambient Air)</td>
<td>75 (13.9)</td>
<td>63 (12.1)</td>
</tr>
<tr>
<td>Baseline – 5 (Low-flow)</td>
<td>232 (42.9)</td>
<td>203 (39.0)</td>
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<tr>
<td>Baseline – 6 (High-flow)</td>
<td>95 (17.6)</td>
<td>98 (18.8)</td>
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<td>Baseline – 7 (MV/ECMO)</td>
<td>131 (24.2)</td>
<td>154 (29.6)</td>
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MV = mechanical ventilation; Sx = symptoms, *Most common = HTN (50.6%), obesity (45.4%), diabetes (30.6%)

Beigel; NEJM 2020. DOI: 10.1056/NEJMoA2007764
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MV = mechanical ventilation; Sx = symptoms, *Most common = HTN (50.6%), obesity (45.4%), diabetes (30.6%)

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

NIPPV = non-invasive positive pressure ventilation

Beigel; NEJM 2020. DOI: 10.1056/NEJMoA2007764
Adaptive COVID Treatment Trial (ACTT-1)

Time to Recovery
Remdesivir 10 d vs. Placebo 15 d
RR 1.29 (95%CI 1.12-1.49; P<0.001)

Time to Recovery
Adjusted for baseline clinical status
RR 1.26 (95%CI 1.09-1.46)

Beigel; NEJM 2020. DOI: 10.1056/NEJMoa2007764
Adaptive COVID Treatment Trial (ACTT-1)

Time to Recovery

Remdesivir 10 d vs. Placebo 15 d
RR 1.29 (95% CI 1.12-1.49; P<0.001)

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

Interaction tests suggest greater benefit (with respect to recovery and mortality) in lower ordinal score categories

Beigel; NEJM 2020. DOI: 10.1056/NEJMoa2007764
Adaptive COVID Treatment Trial (ACTT-1)

Day 15 Clinical Worsening – Remdesivir vs. Placebo

Ambient Air
8.3% vs. 15.7%

Low-flow
10.4% vs. 23.6%

High-flow
30.5% vs. 36.7%

MV/ECMO
10.7% vs. 13.6%

Beigel; NEJM 2020. DOI: 10.1056/NEJMoa2007764
Adaptive COVID Treatment Trial (ACTT-1)

Mortality – Day 15
KM Estimate 6.7% vs. 11.9%
HR 0.55 (95% CI 0.36-0.83)

Mortality – Day 29
KM Estimate 11.4% vs. 15.2%
HR 0.73 (95% CI 0.52-1.03)

KM = Kaplan-Meier

Society of Infectious Diseases Pharmacists
Beigel; NEJM 2020. DOI: 10.1056/NEJMoa2007764
Adaptive COVID Treatment Trial (ACTT-1)

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<tr>
<td>Acute kidney injury</td>
<td>9 (1.7)</td>
<td>17 (3.3)</td>
</tr>
<tr>
<td>Resp failure/distress</td>
<td>64 (12)</td>
<td>100 (19.4)</td>
</tr>
<tr>
<td>Hypotension/shock</td>
<td>9 (1.7)</td>
<td>11 (2.2)</td>
</tr>
<tr>
<td><strong>Non-Serious</strong></td>
<td>276 (51.9)</td>
<td>295 (57.2)</td>
</tr>
<tr>
<td>Anemia/Hgb decrease</td>
<td>42 (7.9)</td>
<td>52 (10.1)</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>55 (10.3)</td>
<td>74 (12.0)</td>
</tr>
<tr>
<td>AST/ALT elevation</td>
<td>30 (5.7)</td>
<td>57 (11.1)</td>
</tr>
<tr>
<td>Lymphocyte decrease</td>
<td>44 (8.3)</td>
<td>54 (10.5)</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. DOI: 10.1056/NEJMoa2007764
Adaptive COVID Treatment Trial (ACTT-1)

- Largely consistent with preliminary report
- 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, not > 10 days
    - Inconsistent trends by quartile, requires further confirmation
- Mortality
  - No statistically significant reduction in mortality
  - Baseline group 5 – lower mortality in remdesivir
- Safety
  - Lower adverse event rate compared to placebo group; well-tolerated

Beigel; NEJM 2020. DOI: 10.1056/NEJMoa2007764
SIMPLE-1 Severe – 5 vs. 10 days

- 408 Screened
  - 5 Ineligible
    - 1 Discharged
    - 5 No treatment
  - Excluded
    - MV/ECMO
    - MODS
      - MODS = multi-organ dysfunction syndrome
- 397 Started
  - 5-Day n = 200
  - 10-Day n = 197

Goldman; NEJM 2020. DOI: 10.1056/NEJMo2015301
SIMPLE-1 Severe – 5 vs. 10 days

- 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>Mean age (SD) – 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>Baseline Status – no. (%)&amp;</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. DOI: 10.1056/NEJMoa2015301
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

P=0.14
Stratified Wilcoxon rank-sum

Adjusted for baseline clinical status

Goldman; NEJM 2020. DOI: 10.1056/NEJMoa2015301

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

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

Goldman; NEJM 2020. DOI: 10.1056/NEJMoa2015301
SIMPLE-1 Severe – 5 vs. 10 days

Caution:
- Post-hoc analysis
- Small subgroups
- Inconsistent trends

Goldman; NEJM 2020. DOI: 10.1056/NEJMoa2015301
## 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>Invasive (N=4)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Noninvasive (N=49)</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Low-flow oxygen (N=107)</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Ambiant air (N=32)</td>
<td>5/6</td>
<td>5/6</td>
</tr>
<tr>
<td>Death</td>
<td>1 (25)</td>
<td>4 (50)</td>
</tr>
<tr>
<td>Invasive</td>
<td>2 (50)</td>
<td>13 (22)</td>
</tr>
<tr>
<td>Noninvasive</td>
<td>6 (12)</td>
<td>19 (33)</td>
</tr>
<tr>
<td>Low-flow oxygen</td>
<td>8 (7)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Ambiant air</td>
<td>2 (6)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Discharged</td>
<td>1 (25)</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Improvement</td>
<td>1 (25)</td>
<td>4 (7)</td>
</tr>
</tbody>
</table>

### Improvement: ACTT-1 Placebo

<table>
<thead>
<tr>
<th></th>
<th>5-day course</th>
<th>10-day course</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIDP</td>
<td>44.3%</td>
<td>44.3%</td>
</tr>
<tr>
<td>Improvement</td>
<td>76.6%</td>
<td>76.6%</td>
</tr>
</tbody>
</table>

Goldman; NEJM 2020. DOI: 10.1056/NEJMo2015301
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. DOI: 10.1056/NEJMoa2015301
SIMPLE-2 Moderate – 10d vs. 5d vs. SOC

612 Screened

596 Randomized

16 Excluded

10-Day n = 197

5-Day n = 199

SOC n = 200

193 Started

191 Started

73 (37.8%) Completed

145 (75.9%) Completed

Median 6 days

Median 5 days

SOC = Standard care

Open-label

Spinner; JAMA 2020. DOI:10.1001/jama.2020.16349
### SIMPLE-2 Moderate – 10d vs. 5d vs. SOC

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>10 Day (n = 197)</th>
<th>5 Day (n = 199)</th>
<th>SOC (n=200)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (IQR) – yr</td>
<td>56 (45-66)</td>
<td>58 (48-66)</td>
<td>57 (45-66)</td>
</tr>
<tr>
<td>Male sex – no. (%)</td>
<td>112 (61)</td>
<td>114 (60)</td>
<td>125 (63)</td>
</tr>
<tr>
<td>Median Sx (IQR) – days</td>
<td>8 (5-11)</td>
<td>8 (5-11)</td>
<td>9 (6-11)</td>
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<td>Hosp. days before RDV (IQR)</td>
<td>2 (1-3)</td>
<td>2 (1-3)</td>
<td>--</td>
</tr>
<tr>
<td>Baseline Status – no. (%)&amp;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ambient air – No care</td>
<td>6 (3)</td>
<td>0</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Ambient air – Medical care</td>
<td>163 (84)</td>
<td>160 (84)</td>
<td>160 (80)</td>
</tr>
<tr>
<td>Low-flow</td>
<td>23 (12)</td>
<td>29 (15)</td>
<td>36 (18)</td>
</tr>
<tr>
<td>High-flow</td>
<td>1 (1)</td>
<td>2 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Steroids</td>
<td>29 (15)</td>
<td>33 (17)</td>
<td>38 (19)</td>
</tr>
</tbody>
</table>

Most common comorbidities: cardiovascular disease (55.1%), hypertension (41.5%), diabetes (38.8%)

Spinner; JAMA 2020. DOI:10.1001/jama.2020.16349
### SIMPLE-2 Moderate – 10d vs. 5d vs. SOC

<table>
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<tr>
<th>Characteristic</th>
<th>10 Day (n = 197)</th>
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<tr>
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<td>163 (84)</td>
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<td>29 (15)</td>
<td>36 (18)</td>
</tr>
<tr>
<td>High-flow</td>
<td>1 (1)</td>
<td>2 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Steroids</td>
<td>29 (15)</td>
<td>33 (17)</td>
<td>38 (19)</td>
</tr>
</tbody>
</table>

Most common comorbidities: cardiovascular disease (55.1%), hypertension (41.5%), diabetes (38.8%)

1° = Day 11 Clinical Status

- 7 – Discharged
- 6 – Inpatient; No care
- 5 – Inpatient; Care
- 4 – Low-flow
- 3 – High-flow
- 2 – MV/ECMO
- 1 – Death

Spinner; JAMA 2020. DOI:10.1001/jama.2020.16349
SIMPLE-2 Moderate – 10d vs. 5d vs. SOC

1° = Day 11 Clinical Status

- 7 – Discharged
- 6 – Inpatient; No care
- 5 – Inpatient; Care
- 4 – Low-flow
- 3 – High-flow
- 2 – MV/ECMO
- 1 – Death

Day 11 – Clinical Status
5-day vs. SOC: OR 1.65 (1.09-2.48); \( P = 0.02 \)
10-day vs. SOC: \( P = 0.18 \)

Day 14 – Clinical Status
5-day vs. SOC: \( P = 0.03 \)
10-day vs. SOC: \( P = 0.03 \)

Day 28 – Clinical Status
5-day vs. SOC: \( P = 0.08 \)
10-day vs. SOC: \( P = 0.03 \)

OR = odd’s ratio; Wilcoxon rank-sum test used if odds assumption not met
Non-primary analyses should be interpreted as exploratory
Type I error risk, multiple comparisons without correction

SIMPLE-2 Moderate – 10d vs. 5d vs. SOC

RDV pts. - 6% less worsening
RDV pts. – 3-4% less worsening

eFigure 1. Change in Clinical Status Over Time

5-Day RDV
10-Day RDV
Standard Care
5-Day RDV
10-Day RDV
Standard Care
5-Day RDV
10-Day RDV
Standard Care
5-Day RDV
10-Day RDV
Standard Care
5-Day RDV
10-Day RDV
Standard Care
SIMPLE-2 Moderate – 10d vs. 5d vs. SOC

Open-label, lack of matching placebo

Daily discharge rates higher day after therapy completion

Spinner; JAMA 2020. DOI:10.1001/jama.2020.16349
SIMPLE-2 Moderate – 10d vs. 5d vs. SOC

Take home points:
• Significant improvement day 11 status with 5-day vs. SOC
  • Not seen with 10-day group; open-label design potential influence
• Lower disease progression with remdesivir (consistent with ACTT-1)
• Low incidence of progression to severe disease/mortality overall (≤2%)

• Safety
  • Any AE higher in 10-day (59%) vs. 5-day (51%) vs. SOC (47%)
  • Similar grade ≥ 3 (12% vs. 10% vs. 12%)
  • Low remdesivir discontinuation (4% vs. 2%)

Spinner; JAMA 2020. DOI:10.1001/jama.2020.16349
WHO Solidarity – RDV Arm

- 405 sites, 30 countries, N= 11,266 randomized
- HCQ
- LPV/r
- IFN β1a
- RDV
- Discontinued for futility

- Remdesivir n = 2,750
- Control n = 2,725
- No/uncertain consent n = 7
- ITT n = 2,743
- ITT n = 2,708
- Crossover to RDV – 2%
- No/uncertain consent n = 17

Pan; NEJM 2020. DOI: 10.1056/NEJMoa2023184
### WHO Solidarity – RDV Arm

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RDV (n = 2,743)</th>
<th>SOC (n=2,708)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 70 yr – n (%)</td>
<td>2,243 (81.8)</td>
<td>2,239 (82.6)</td>
</tr>
<tr>
<td>Age ≥ 70 yr – n (%)</td>
<td>500 (18.2)</td>
<td>469 (17.3)</td>
</tr>
<tr>
<td>Male sex – no. (%)</td>
<td>1,706 (62.1)</td>
<td>1,725 (63.7)</td>
</tr>
<tr>
<td>Baseline Status – no. (%)&amp;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No oxygen at entry</td>
<td>661 (24.1)</td>
<td>664 (24.5)</td>
</tr>
<tr>
<td>On oxygen at entry</td>
<td>1,828 (66.6)</td>
<td>1,811 (66.8)</td>
</tr>
<tr>
<td>Already ventilated</td>
<td>254 (9.2)</td>
<td>233 (8.6)</td>
</tr>
<tr>
<td>Steroids</td>
<td>1,310 (47.8)</td>
<td>1,288 (47.6)</td>
</tr>
<tr>
<td>Convalescent Plasma</td>
<td>52 (1.9)</td>
<td>58 (2.1)</td>
</tr>
</tbody>
</table>

Common comorbidities: diabetes (25.2%), cardiovascular disease (20.8%), hypertension (5.4%)
WHO Solidarity – RDV Arm

Overall Population

By Ventilation Status

Ventilated
- 43.0% Remdesivir
- 37.8% Control
Age-stratified rate ratio, 1.20 (95% CI 0.89-1.64)
p=0.24 by log-rank test

Not ventilated
- 10.6% Control
- 9.4% Remdesivir
Rate ratio, 0.86 (95% CI 0.72-1.04), p=0.13

Pan; NEJM 2020. DOI: 10.1056/NEJMoa2023184
## WHO Solidarity – RDV Arm

### Subgroup

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Remdesivir</th>
<th>Control</th>
<th>Rate Ratio for Death (99% CI; 95% CI for totals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No supplemental oxygen</td>
<td>11/66</td>
<td>12/64</td>
<td>0.90 (0.31–2.58)</td>
</tr>
<tr>
<td>Low-flow or high-flow oxygen</td>
<td>19/323</td>
<td>21/232</td>
<td>0.85 (0.66–1.09)</td>
</tr>
<tr>
<td>Ventilation</td>
<td>98/254</td>
<td>71/233</td>
<td>1.20 (0.98–1.80)</td>
</tr>
<tr>
<td>Stratified total: Solidarity</td>
<td>301/2743</td>
<td>303/2708</td>
<td>0.94 (0.80–1.10)</td>
</tr>
</tbody>
</table>

### ACTTT-1 (stratified according to 4 ordinal score levels)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Remdesivir</th>
<th>Control</th>
<th>Rate Ratio for Death (99% CI; 95% CI for totals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No supplemental oxygen</td>
<td>3/75</td>
<td>1/63</td>
<td>0.82 (0.10–6.61)</td>
</tr>
<tr>
<td>Low-flow oxygen</td>
<td>9/232</td>
<td>21/203</td>
<td>0.30 (0.11–0.81)</td>
</tr>
<tr>
<td>High-flow oxygen or noninvasive ventilation</td>
<td>19/95</td>
<td>20/98</td>
<td>1.02 (0.44–2.34)</td>
</tr>
<tr>
<td>Invasive ventilation</td>
<td>28/111</td>
<td>29/154</td>
<td>1.13 (0.57–2.23)</td>
</tr>
<tr>
<td>Stratified total: ACTTT-1</td>
<td>59/333</td>
<td>77/318</td>
<td>0.82 (0.58–1.16)</td>
</tr>
</tbody>
</table>

### Trials with few deaths (and randomization ratio of 2:1)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Remdesivir</th>
<th>Control</th>
<th>Rate Ratio for Death (99% CI; 95% CI for totals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wuhan: low-flow oxygen</td>
<td>11/129</td>
<td>11/127</td>
<td>0.81 (0.21–3.07)</td>
</tr>
<tr>
<td>Wuhan: high-flow oxygen or ventilation</td>
<td>11/29</td>
<td>11/30</td>
<td>1.40 (0.20–9.52)</td>
</tr>
<tr>
<td>International: no supplemental oxygen</td>
<td>5/384</td>
<td>5/383</td>
<td>0.64 (0.10–3.94)</td>
</tr>
<tr>
<td>Stratified total: 2:1 trials</td>
<td>27/542</td>
<td>27/548</td>
<td>0.86 (0.42–1.77)</td>
</tr>
</tbody>
</table>

### Risk groups (calculated by summation of relevant strata)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Remdesivir</th>
<th>Control</th>
<th>Rate Ratio for Death (99% CI; 95% CI for totals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower risk: strata with no ventilation</td>
<td>213/360</td>
<td>222/377</td>
<td>0.80 (0.63–1.01)</td>
</tr>
<tr>
<td>Higher risk</td>
<td>156/507</td>
<td>125/505</td>
<td>1.16 (0.85–1.60)</td>
</tr>
<tr>
<td>Stratified total</td>
<td>378/3818</td>
<td>408/3782</td>
<td>0.91 (0.79–1.05)</td>
</tr>
</tbody>
</table>

### Heterogeneity between trials (Solidarity vs. ACTTT-1 vs. 2:1 trials): $\chi^2_{1}=0.5$

### Remdesivir Better | Control Better

Pan; NEJM 2020.
Remdesivir conferred no benefit towards reducing hospital length of stay or progression to intubation.
Take home points:

• Largest trial to date
  • Fivefold larger than ACTT-1
  • Open-label design (risk of bias)

• No benefit of remdesivir on mortality
  • Meta-analysis lower severity subgroup potential benefit

• No benefit observed for hospital duration or intubation rate
Adaptive COVID Treatment Trial (ACTT-2)

- Assessed: 1067 patients
- Excluded: 34 patients
- Ineligible: 29 patients
- Not enrolled: 5 patients

Randomized: 1033 patients

- Placebo: n = 518
- Baricitinib: eGFR ≥ 60 = 4mg, eGFR < 60 = 2mg

As assigned: 507 patients (98.4%)

Terminated early: 61 patients; 11.8%

ITT = intention-to-treat

- Placebo: n = 518
- Baricitinib: n = 515

As assigned: 509 patients (98.3%)

Terminated early: 74 patients; 14.3%

Kalil; NEJM 2020. DOI: 10.1056/NEJMoa2031994
## Adaptive COVID Treatment Trial (ACTT-2)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baricitinib (n = 515)</th>
<th>Placebo (n = 518)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD) – yr</td>
<td>55.0 (15.4)</td>
<td>55.8 (16.0)</td>
</tr>
<tr>
<td>Male sex – no. (%)</td>
<td>319 (61.9)</td>
<td>333 (64.3)</td>
</tr>
<tr>
<td>Median Sx (IQR) – days</td>
<td>8 (5-10)</td>
<td>8 (5-11)</td>
</tr>
<tr>
<td>Comorbidities ≥ 2* – no. (%)</td>
<td>284 (57.3)</td>
<td>285 (57.2)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>87 (16.9)</td>
<td>104 (20.0)</td>
</tr>
<tr>
<td>Baseline Status – no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline – 4 (Ambient Air)</td>
<td>70 (13.6)</td>
<td>72 (13.9)</td>
</tr>
<tr>
<td>Baseline – 5 (Low-flow)</td>
<td>288 (55.9)</td>
<td>276 (53.3)</td>
</tr>
<tr>
<td>Baseline – 6 (High-flow)</td>
<td>103 (20)</td>
<td>113 (21.8)</td>
</tr>
<tr>
<td>Baseline – 7 (MV/ECMO)</td>
<td>54 (10.7)</td>
<td>57 (11.0)</td>
</tr>
</tbody>
</table>

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**

NIPPV = non-invasive positive pressure ventilation

Kalil; NEJM 2020. DOI: 10.1056/NEJMoa2031994
Adaptive COVID Treatment Trial (ACTT-2)

**Time to Recovery**
Baricitinib 7 d vs. Placebo 8 d
RR 1.16 (95%CI 1.01-1.32; P=0.03)

**Length of Stay**
Baricitinib 8 d (IQR 5-15)
Placebo 8 d (IQR 5-20)

**28-d Mortality**
HR 0.65 (95%CI 0.39-1.09)

**New MV/ECMO**
Baricitinib n = 46 (10%; 95%CI 8-13%)
Placebo n = 70 (15%; 95%CI 12-19%)

Confidence intervals unadjusted for multiplicity
Secondary analyses should not be used to infer definitive effects

Kali; NEJM 2020. DOI: 10.1056/NEJMoa2031994
Adaptive COVID Treatment Trial (ACTT-2)

**Ambient Air**

![Graph showing proportion recovered over days for Ambient Air treatment groups: Placebo + RDV, Baricitinib + RDV.](Graph)

**Low-flow**

![Graph showing proportion recovered over days for Low-flow treatment groups: Placebo + RDV, Baricitinib + RDV.](Graph)

**High-flow**

![Graph showing proportion recovered over days for High-flow treatment groups: Placebo + RDV, Baricitinib + RDV.](Graph)

**MV/ECMO**

![Graph showing proportion recovered over days for MV/ECMO treatment groups: Placebo + RDV, Baricitinib + RDV.](Graph)

Kalil; NEJM 2020. DOI: 10.1056/NEJMoa2031994
Adaptive COVID Treatment Trial (ACTT-2)

Day 15 Clinical Worsening – Baricitinib vs. Placebo

Ambient Air
10% vs. 8.3%

Low-flow
6.9% vs. 9.1%

High-flow
16.5% vs. 29.2%

MV/ECMO
11.1% vs. 12.3%
## Adaptive COVID Treatment Trial (ACTT-2)

Generally well tolerated; All AEs/SAEs significantly lower in baricitinib arm

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Baricitinib (n = 507)</th>
<th>Placebo (n = 509)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Events – n (%)</td>
<td>187 (36.9)</td>
<td>220 (43.2)</td>
</tr>
<tr>
<td>GFR decrease/AKI</td>
<td>71 (14.0)</td>
<td>75 (14.8)</td>
</tr>
<tr>
<td>Anemia/Hgb decrease</td>
<td>54 (10.6)</td>
<td>58 (11.4)</td>
</tr>
<tr>
<td>Transaminase increase</td>
<td>15 (2.9)</td>
<td>30 (5.9)</td>
</tr>
<tr>
<td>VTE</td>
<td>21 (4.1)</td>
<td>16 (3.1)</td>
</tr>
<tr>
<td>DVT</td>
<td>11 (2.2)</td>
<td>9 (1.8)</td>
</tr>
<tr>
<td>Serious Adverse Events</td>
<td>81 (16)</td>
<td>107 (21)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>5 (1)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Infection</td>
<td>30 (5.9)</td>
<td>57 (11.2)</td>
</tr>
</tbody>
</table>

Hgb = hemoglobin; VTE = venous thromboembolism

Kalil; NEJM 2020. DOI: 10.1056/NEJMoa2031994
Adaptive COVID Treatment Trial (ACTT-2)

- Statistically significant reduction in time to recovery
  - Clinical significance questionable (1-day reduction, driven by O2 requirement)
  - No effect on key secondary endpoints (length of stay, mortality)
  - Prevention of progression in high-flow patients; further investigated in ACTT-4

- Safety
  - Lower adverse event rate compared to placebo group; well-tolerated
  - No increased rates of venous thromboembolism or infectious complications in baricitinib arm

Kalil; NEJM 2020. DOI: 10.1056/NEJMoA2031994
### PINETREE Study – Early Outpatient Therapy

**Inclusion:**
- ≥ 12 years with risk factor
- ≥ 60 years
- ≤ 7 days symptom onset
- ≤ 4 days PCR (+)

**Exclusions:**
- Perceived need supp. O2/hospitalization
- Previous therapy/hospitalization
- COVID-19 vaccination

**Risk Factors:**
- Hypertension
- CVD or CVA
- Diabetes mellitus
- BMI ≥ 30
- Mild-moderate CKD
- Chronic liver disease
- Chronic lung disease
- Cancer
- Sickle cell disease

**Study Details:**
- Total Assessed: 630
- Randomized: 584
- Remdesivir: n = 292
- Placebo: n = 292
- No dose: Remdesivir: n = 9 (3.1%)
- No dose: Placebo: n = 13 (4.4%)

**Analysis:**
- Remdesivir: n = 283
- Placebo: n = 279

Gottlieb; NEJM 2021. DOI: 10.1056/NEJMoa2116846
## PINETREE Study – Early Outpatient Therapy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baricitinib (n = 279)</th>
<th>Placebo (n = 283)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD) – yr</td>
<td>50 (15)</td>
<td>51 (15)</td>
</tr>
<tr>
<td>Female sex – no. (%)</td>
<td>131 (47)</td>
<td>138 (48.8)</td>
</tr>
<tr>
<td>Body Mass Index (SD)</td>
<td>31.2 (6.7)</td>
<td>30.8 (5.8)</td>
</tr>
<tr>
<td>Median Sx (IQR) – days</td>
<td>5 (3-6)</td>
<td>5 (4-6)</td>
</tr>
<tr>
<td>Comorbidities – no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>173 (62)</td>
<td>173 (61.1)</td>
</tr>
<tr>
<td>Obesity</td>
<td>154 (55.2)</td>
<td>156 (55.1)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>138 (49.5)</td>
<td>130 (45.9)</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>67 (24)</td>
<td>68 (24)</td>
</tr>
<tr>
<td>Immune compromise</td>
<td>14 (5)</td>
<td>9 (3.2)</td>
</tr>
</tbody>
</table>

### Outcomes
- 1° – D28 hospitalization/death
- 2° –
  - D14 Medical visit/death
  - D28 Medical visit/death
  - D7 Viral load reduction
  - Time to mild/absent symptoms

Gottlieb; NEJM 2021. DOI: 10.1056/NEJMoa2116846
PINETREE Study – Early Outpatient Therapy

Hospitalization/Death

Remdesivir 0.7% vs. Placebo 5.3%
aHR 0.13 (95%CI 0.03-0.59; P=0.008)

Cox-proportional hazard model adjusted for SNF residence, age, location

D14 Medical Visits/Death

Remdesivir 2/246 (0.8%)
Placebo 20/252 (7.9%)

D28 Medical Visits/Death

Remdesivir 4/246 (1.6%)
Placebo 21/252 (8.3%)

D14 Symptom Alleviation

Remdesivir 61/169 (36.1%)
Placebo 33/165 (20.0%)
RR 1.92 (95%CI 1.26-2.94)

Gottlieb; NEJM 2021. DOI: 10.1056/NEJMoa2116846
PINETREE Study – Early Outpatient Therapy

Wang et al.

Gottlieb; NEJM 2021. DOI: 10.1056/NEJMoa2116846
Wang; Lancet 2020. DOI: 10.1016/S0140-6736(20)31022-9
PINETREE Study – Early Outpatient Therapy

• Statistically significant reduction COVID-19 hospitalizations
  • Nsp12 polymerase highly conserved compared to spike protein
  • Effect size would likely be diminished in vaccinated or low-risk populations; Operationally challenging
  • Immunocompromised patients underrepresented

• Significantly higher symptom resolution by day 14 with remdesivir
• No impact on virologic outcomes at day 7, similar to previous findings

• Safety
  • No new safety signals, remdesivir was well tolerated

Gottlieb; NEJM 2021. DOI: 10.1056/NEJMoa2116846
<table>
<thead>
<tr>
<th>Variable</th>
<th>Lancet Severe RCT</th>
<th>ACTT-1</th>
<th>SIMPLE-1 Severe</th>
<th>SIMPLE-2 Moderate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample, (n)</td>
<td>237</td>
<td>1062</td>
<td>397</td>
<td>596</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>8 (5-11)</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>11.4</td>
<td>15.2</td>
</tr>
<tr>
<td>TTCR (days)</td>
<td>21</td>
<td>23</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>AEs Discontinue Tx, n (%)</td>
<td>18 (12)</td>
<td>4 (5)</td>
<td>52 (9.6)</td>
<td>70 (13.4)</td>
</tr>
</tbody>
</table>

Sx = symptoms; TTCR = time to clinical recovery; AE = adverse effects; Tx = treatment
**14-day mortality data; *Recovery defined differently across trials

Available (Final) Results

Wang; Lancet 2020. DOI: 10.1016/S0140-6736(20)31022-9
Beigel; NEJM 2020. DOI: 10.1056/NEJMoa2007764
Goldman; NEJM 2020. DOI: 10.1056/NEJMoa2015301
Spinner; JAMA 2020. DOI:10.1001/jama.2020.16349
### Available Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>SOLIDARITY</th>
<th>ACTT-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample, (n)</td>
<td>5451</td>
<td>1033</td>
</tr>
<tr>
<td>Severity</td>
<td>Hospitalized</td>
<td>Hypoxia/PNA/Supp. O2</td>
</tr>
<tr>
<td>Sx duration, days (IQR)</td>
<td>Unspecified</td>
<td>8 (5-10)</td>
</tr>
<tr>
<td>Intervention</td>
<td>10-day SOC</td>
<td>RDV + bari</td>
</tr>
<tr>
<td>Mortality (28d), (%)</td>
<td>12.5*</td>
<td>12.7*</td>
</tr>
<tr>
<td>TTCR (days)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>AEs Discontinue Tx, n (%)</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

Sx = symptoms; TTCR = time to clinical recovery; AE = adverse effects; Tx = treatment; SOC = standard of care
*SOLIDARITY: In-hospital mortality;

Kalil; NEJM 2020. DOI: 10.1056/NEJMoa2031994
Pan; NEJM 2020. DOI: 10.1056/NEJMoa2023184
Clinical Summary

• Remdesivir significantly reduces time to clinical recovery
  • Benefit most apparent in baseline low-flow patients; modest benefit for moderate disease
  • Minimal/no benefit observed in ≥ high-flow; Longer follow-up data needed
• No mortality benefit in overall population
  • Possible benefit in lower risk groups (patients requiring low-flow)
• Data not definitively supportive of 10-day symptom cutoff, earlier therapy plausibly better
• In patients who derive benefit, 5-days = 10-days
• Early outpatient therapy significantly reduces COVID-19 hospitalizations
  • Data in unvaccinated, symptomatic patients at risk for disease progression
• Serious and non-serious adverse events similar/lower than placebo
  • Well-tolerated overall
1. 3/24/2020 – Original version posted
2. 4/5/2020 – Community transmission case report; ongoing trial info updated
3. 4/12/2020 – Compassionate use case series added; ongoing trial info updated
4. 4/17/2020 – Updated trial info
5. 4/29/2020 – Lancet Severe Trial, NIAID/SIMPLE prelim data, Updated trial info
6. 5/1/2020 – Emergency Use Authorization
7. 6/6/2020 – ACTT-1, SIMPLE-1, SIMPLE-2 top-line results, trials updated
8. 7/2020 – RDV/HCQ interaction, Phase 2/3 peds
9. 9/5/2020 – SIMPLE-2 results, EUA expansion, updated trial info
10. 10/16/2020 – Additional MOA, Updated in vitro data, resistance, SARS-CoV-2 animal data, Final ACTT-1, Solidarity, clinical trials data
11. 12/14/2020 – ACTT-2, SOLIDARITY final results
12. 12/24/2021 – PINETREE results
Questions

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