New COVID-19 Antiviral Therapies

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COVID-19: why do we still need antivirals?

1  Need for greater sterilising potency
   - Persistent or relapsing disease in immunosuppressed
   - (Rebounds ??)

2  Resistance
   - mAbs (well-characterised)
   - Small molecules (possible)

3  Pandemic Preparedness
   - New zoonotic transmissions
<table>
<thead>
<tr>
<th>Population</th>
<th>N</th>
<th>Viral rebound</th>
<th>Clinical rebound</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPIC HR RCT</td>
<td>NMV/r placebo</td>
<td>1106</td>
<td>2.3%</td>
</tr>
<tr>
<td>AGILE CST-2 RCT</td>
<td>MOL placebo</td>
<td>90</td>
<td>3.3%</td>
</tr>
<tr>
<td>ACTIV-2 RCT</td>
<td>Untreated</td>
<td>563</td>
<td>31%</td>
</tr>
<tr>
<td>SCORPIO SR RCT</td>
<td>ESV placebo</td>
<td>590</td>
<td>7.8%</td>
</tr>
<tr>
<td>Wang et al* cohort</td>
<td>NMVr MOL</td>
<td>11270</td>
<td>5.4%</td>
</tr>
<tr>
<td>Wang et al* cohort</td>
<td>NMVr MOL</td>
<td>2374</td>
<td>8.59%</td>
</tr>
<tr>
<td>Hong Kong cohort</td>
<td>NMVr MOL untreated</td>
<td>242</td>
<td>6.6%</td>
</tr>
<tr>
<td>Hong Kong cohort</td>
<td>NMVr MOL untreated</td>
<td>195</td>
<td>1.0%</td>
</tr>
<tr>
<td>Hong Kong cohort</td>
<td>NMVr MOL untreated</td>
<td>746</td>
<td>0.8%</td>
</tr>
</tbody>
</table>

Wong et al. Lancet Infect Dis. 2023 Jun;23(6):683-695
Wong et al. JAMA Netw Open. 2022;5(12):e2245086
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COVID-19: why do we still need antivirals?

1 Need for greater sterilising potency
   - Persistent or relapsing disease in immunosuppressed
   - (Rebounds ??)

2 Resistance
   - mAbs (well-characterised)
   - Small molecules (possible)

3 Pandemic Preparedness
   - New variants
   - New zoonotic transmissions
Schematic – the Optimal Antiviral

Potent Small Molecules Or Combination Therapy

Genetic barrier

Breadth & coverage

mAbs

potency

Combi mAbs
COVID-19 Guidelines - Use of DAAs in Adults

**Community**

*Standard risk*

*High risk*

**Hospitalised**

*Hypoxia*

*Critical, ventilated*

- Strong for / A / Recommended
- Conditional or weak for / B or C / alternative
- Conditional against / weak against
- Strong against / not recommended

SARS-CoV-2 test positive within specified window
Symptomatic disease in adult patients

* Avoid in children and pregnancy

https://app.magicapp.org/#/guideline/nBkO1E/rec/LwrMyv
https://app.magicapp.org/#/guideline/L4Qb5n/section/LAJvRn

WHO 13 Jan 2023
NIH 8 Aug 2022
NICE 29 Mar 2023
AWMF 12 Sep 2022
NCET 27 Mar 2023
Clinical Trial Endpoints

1 Death and hospitalisation
   - Placebo arms of PINETREE (5.3%), EPIC-HR (7%) → PANORAMIC (1%)
   - Difficult/impossible to include placebo in high-risk populations

2 Participant-reported symptoms
   - Open-label designs?
   - Which questionnaires, how and when to evaluate?

3 Virology
   - RNA vs infectious virus?
   - Qualitative vs titre vs elimination rates?
   - Limited value for predicting clinical utility

Virology and clinical endpoints not always concordant
<table>
<thead>
<tr>
<th>Drug</th>
<th>N</th>
<th>Population</th>
<th>Clinical benefit</th>
<th>Virological signal</th>
</tr>
</thead>
<tbody>
<tr>
<td>PINETREE RDV</td>
<td>III</td>
<td>Outpatient</td>
<td>Y ▼</td>
<td>N R</td>
</tr>
<tr>
<td>AGILE CST-2 MOL</td>
<td>I/II</td>
<td>Outpatient</td>
<td>N ▼</td>
<td>Y R</td>
</tr>
<tr>
<td>MoveOut MOL</td>
<td>III</td>
<td>Outpatient</td>
<td>Y DHW</td>
<td>Y R (D3, D5 only)</td>
</tr>
<tr>
<td>PANORAMIC MOL</td>
<td>IV</td>
<td>Outpatient</td>
<td>N DHW Y §</td>
<td>Y R (D7; P=0.039)</td>
</tr>
<tr>
<td>EPIC-HR NMV/r</td>
<td>III</td>
<td>Outpatient</td>
<td>Y DHW</td>
<td>Y R (D5; 1 log if started in 72h; P&lt;0.001)</td>
</tr>
<tr>
<td>SCORPIO-SR Ensitrelvir</td>
<td>II/III</td>
<td>Outpatient</td>
<td>Y ◊</td>
<td>Y CR</td>
</tr>
<tr>
<td>SPRINT (Enanta) EDP-235</td>
<td>II</td>
<td>Outpatient</td>
<td>Y ◊</td>
<td>N CR</td>
</tr>
<tr>
<td>Pardes PBI-0451</td>
<td>II</td>
<td>Outpatient</td>
<td>N ◊</td>
<td>N CR</td>
</tr>
<tr>
<td>MOONSONG AT-527</td>
<td>II</td>
<td>Outpatient</td>
<td>N</td>
<td>N C (all)</td>
</tr>
<tr>
<td>MORNINGSKY AT-527</td>
<td>III</td>
<td>Outpatient</td>
<td>N § ▼</td>
<td>hosp</td>
</tr>
</tbody>
</table>

▼ FLU-PRO Plus
◊ FDA instrument
§ other symptom scale
DHW deaths, hospitalisations and/or WHO score
C infectious virus
R RNA titre
### Participant-reported Symptoms

**FLU-PRO Plus**
- Originally severity (5-point scale) & frequency of 34 symptoms over 6 domains - nose, throat, eyes, respiratory, gastrointestinal, systemic
- Senses (taste & smell) added

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#### Trials
- COMET-ICE
- PINETREE

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**EPICC cohort (N=226)**
Mar 2020- Jun 2021
mean domain and total scores

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Richard et al. Open Forum Infect Dis, 2021;8:ofab517,
Antiviral Therapy – potential targets

1. Binding to ACE2
2. Direct fusion
3. RNA release
4. Translation
5. Proteolysis (3CLpro and PLpro)
6. Replication and translation
7. Packaging and viral assembly
8. Release

Nirmaltrelvir/r
Ensitrelvir (S-217622)
PBI-0451
EDP-235
ALG 097558
CDI-45205
others

Remdesivir
GS-5245 and VV116

Molnupiravir
Favipiravir

mAbs
Ab-like molecules

Others:
siRNA
Gene therapy
etc, etc

Su et al. Fundamental Research 2021;1(2): 151-165
Antibodies – not all the same

- Convalescent plasma vs mAbs vs bnAbs
- Binding sites
- Neutralising activity – neutralising potency vs breadth
- Route, dose and indication (treatment vs prophylaxis)
- Pharmacokinetics
- ADE and ADCC

- Bamlanivimab/ Etesevimab
- Casirivimab/ Imdevimab
- Tixagevimab/ Cilgavimab
- Sotrovimab
- Regdanvimab
- Bebtelovimab
- AZD5156/AZD3152
- SA-58
- Nanobodies
- Sherpabodies (mimetic) (eg TriSb92)
Oral versions of Remdesivir?

Remdesivir GS-5734

Obeldesivir GS-5245

GS-441524

VV116/ Deuremidivir Shanghai Junshi

Deb et al. Pharmaceuticals. 2021; 14(7):655
RESULTS

A total of 822 participants underwent randomization, and 771 received VV116 (384 participants) or nirmatrelvir–ritonavir (387 participants). The noninferiority of VV116 to nirmatrelvir–ritonavir with respect to the time to sustained clinical recovery was established in the primary analysis (hazard ratio, 1.17; 95% confidence interval [CI], 1.01 to 1.35) substantially between the two groups. No participants in either group had died or had had progression to severe Covid-19 by day 28. The incidence of adverse events was lower in the VV116 group than in the nirmatrelvir–ritonavir group (67.4% vs. 77.3%).
Gilead Sciences Statement on Phase 3 Obeldesivir Clinical Trials in COVID-19: BIRCH Study to Stop Enrollment While OAKTREE Study Nears Full Enrollment

Foster City, Calif., September 28, 2023 – Gilead Sciences, Inc. (Nasdaq: GILD) today announced that it has stopped patient enrollment in BIRCH (Study GS-US-611-6273), a Phase 3 study evaluating the efficacy and safety of obeldesivir compared with placebo in non-hospitalized participants who are at high risk for developing severe COVID-19. This decision is based on lower-than-expected COVID-19 incidence rates and related hospitalizations or all-cause death by Day 29, which are primary endpoints in the study. The decision does not reflect any safety or efficacy concerns. Patients already enrolled will continue in the study which remains blinded.

The decision to stop enrolling patients in the BIRCH study does not impact the OAKTREE study (GS-US-611-6549), a Phase 3 study evaluating the safety and efficacy of obeldesivir compared with placebo in non-hospitalized participants without risk factors for developing severe COVID-19. OAKTREE is rapidly approaching full enrollment and will continue to enroll patients in the United States and Japan. Data from
Antiviral Therapy – potential targets

mAbs
Ab-like molecules

Nirmaltrelvir/r
Ensitrelvir (S-217622)
PBI-0451
EDP-235
ALG 097558
CDI-45205
others

Remdesivir
GS-5245 and VV116

Molnupiravir
Favipiravir

Others:
siRNA
Gene therapy
e tc, etc
Molnupiravir

Molnupiravir is a prodrug

.. incorporated into mRNA ....

.. and inducing error catastrophe....

Molnupiravir is converted to its active form molnupiravir triphosphate (MTP) in the cell

1. Translation of viral polymerase protein (RdRp)
2. MTP competes with natural nucleotides, especially CTP
3. MTP is incorporated in the mRNA causing the accumulation of mutations and viral inviability
Hallmark of molnupiravir treatment detectable in vivo

Mean transition/transversion ratio of SARS-CoV-2 significantly increases over time with molnupiravir but not placebo

Treatment allocation

- **placebo** n = 65
- **molnupiravir** n = 59

****$P \leq 0.0001$, ***$P \leq 0.001$, ns = $P > 0.05$

Donovan-Banfield et al., ResearchSquare 2022
Predicted amino acid profile shows increased diversity over time

Donovan-Banfield et al., Nat Comm 2022; 2022 Nov 26;13(1):7284
PK: Non-plasma:Plasma Ratios ($R_{NP:P}$)

**NHC (Molnupiravir)**

![Graph showing the PK profile of NHC (Molnupiravir) across different sample matrices: Saliva, Nasal secretions, and Tears for different dose times.](image)

<table>
<thead>
<tr>
<th>Sample Matrix</th>
<th>Saliva</th>
<th>Tears</th>
<th>Nasal</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHC ($R_{NP:P}$)</td>
<td>Overall [median (range)]</td>
<td>Overall [median (range)]</td>
<td>Overall [median (range)]</td>
</tr>
<tr>
<td>Saliva</td>
<td>0.03 (0.01-0.11, 60%; n=16)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nasal secretions</td>
<td>0.21 (0.05-0.73, 70%; n=17)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tears</td>
<td>0.22 (0.09-1.05, 92%; n=12)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* n=3, † n=2, ‡ n=1

*NHC $R_{NP:P}$, expressed as geometric mean (CV%) unless stated otherwise.*

**Sample Matrix**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Saliva</th>
<th>Tears</th>
<th>Nasal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nirmatrelvir</td>
<td>0.18 (45)</td>
<td>0.86 (20)</td>
<td>0.70 (33)</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>0.008 (20)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* Fitzgerald et al CID 2022 Aug 24;75(1):e525-e528
Dickinson et al. Int Workshop Clin Pharm Antiviral Ther Sept 2023 Rome
Ensitrelvir – Scorpio SR

**Primary Endpoint – symptom resolution**

5 symptoms (prespecified)

Subgroup within 72h of symptom onset

Ensitrelvir 125mg - approx 1 day faster

Ensitrelvir 125mg - 29h faster

Uehara et al CROI 2023 OA-9
Long COVID Symptoms, ≤120 hours

Definition for presence of Long COVID symptoms in post-hoc analysis

- Symptoms listed in **14 COVID-19 symptom questionnaire**
  - At least 2 consecutive time points with a mild or more severe symptom continuing from the last observation in the follow up (e.g., Day 21) to Day 169

- Symptoms listed only in **PASC questionnaire**
  - One mild or more severe symptom at Day 85 OR Day 169

- Relationship with COVID-19: Yes (related) or unknown symptoms (exclude No (not related))

### Proportion with ongoing symptoms (14 COVID-19 symptoms)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo</th>
<th>Ensitrelvir 125 mg</th>
<th>Ensitrelvir 250 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>218</td>
<td>232</td>
<td>216</td>
</tr>
<tr>
<td>Percentage</td>
<td>25%</td>
<td>10%</td>
<td></td>
</tr>
</tbody>
</table>

### Proportion of 4 neurological symptoms in PASC Questionnaire

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo</th>
<th>Ensitrelvir 125 mg</th>
<th>Ensitrelvir 250 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>331</td>
<td>338</td>
<td>317</td>
</tr>
<tr>
<td>Percentage</td>
<td>26%</td>
<td>*</td>
<td>9%</td>
</tr>
</tbody>
</table>

### Subpopulation of patients who have high symptom score for 14 symptoms at baseline

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo</th>
<th>Ensitrelvir 125 mg</th>
<th>Ensitrelvir 250 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>175</td>
<td>180</td>
<td>148</td>
</tr>
<tr>
<td>Percentage</td>
<td>33%</td>
<td>*</td>
<td>26%</td>
</tr>
</tbody>
</table>

---

*P value by Fisher’s exact test <0.05  *high symptom score is defined as the total score of 14 symptoms at baseline ≥ 9

PASC= post-acute sequelae of SARS-CoV-2

Uehara et al CROI 2023
**EDP-235 : Change in Symptom Scores**

**3CL\textsuperscript{pro} inhibitor**

**SPRINT study (Phase II); N ~ 200**

**EDP-235 200mg vs 400mg vs placebo**

14 symptoms
Within 5d onset

14 symptoms
Within 3d onset

6 symptoms
Within 3d onset

No difference in VL reduction between treatment arms and placebo
(subgroup with BL VL >5 log had reduction of 0.4 log over placebo at 3d)

https://ir.enanta.com/events-presentations
May 8 2023 and Sept 12 2023
Pomotrelvir (PBI-0451):

- 3CL\textsuperscript{pro} inhibitor
- Phase II, mild-moderate disease (N = 242), non-hospitalised
- Within 5d of symptoms

**Virology**
- Negative infectious virus at D3 * - pomotrelvir (70%) vs placebo (63%)
- No difference in infectious virus or RNA at D2, 3, or 5

**Symptoms**
- No difference in FDA symptom score (14) or (12) or (5)

Viral titres lower, clearance and symptom resolution more rapid than anticipated

Clinical Development halted

* Primary endpoint

Kearney et al CROI 2022 (LB470)

Bemnifosbuvir (AT-527)

- RdRp inhibitor (guanosine analogue)
- Broad spectrum

MOONSONG (Phase 2, non-hospitalised)
- No difference in viral (RNA) clearance between 2 doses of AT-527 and placebo
- Potential signal in (prespecified) subgroup of participants with underlying medical conditions

MORNINGSKY (Phase 3, non-hospitalised)
- Closed early – bemnifosbuvir (137) vs placebo (70)
- Time-to-symptom alleviation (primary endpoint) not met
- Exploratory analysis (unadjusted) – 71% reduction in hospitalisations

SUNRISE-3

https://ateapharma.com/covid-19/bemnifosbuvir/
Rational Selection of Combinations

- Small molecule + small molecule
- mAb + small molecule
- Antiviral + Host-targeted

Rational design of regimens, based on:
- Additivity, synergy
- Parity of evidence
- Operational deployment

Argues for publicly-funded platforms!

New SARS-CoV-2 Antivirals

- **Continued need for better drugs**
  - greater potency
  - fewer DDIs

- **Case for evaluating combinations**

- **Importance of publicly-funded trial platforms**
  - able to develop protocols ‘at-risk’
  - access candidates from academia and small-medium biotech
  - rational design and timely evaluation of combinations

- **Access, access, access**
  - testing
  - participation in clinical trials
  - affordable treatments
Southampton Clinical Trials Unit
Gareth Griffith
Sean Ewings
Geoff Saunders
Andrea Corkhill
Nicky Downs
Emma Knox
Anna Song
Calley Middleton

NIHR CRFs
Manchester – Shazaad Ahmad
Southampton – Christopher Edwards
Preston – Denis Hadjiliannakis
London – Jimstan Periselneris

Jasmine Martin
Sara Gibbons
Daryl Hodget
Daniel Seddon
Steve Potter
Vicky Winters
Val Almond

Catia Marzolini
Fiona Marra
Alison Boyle

David Back
Alice Tseng
Tessa Senneker
Pierre Giguere
Sarita Boyd
Alice Pau
Kim Scarsi