Bemcentinib, an oral AXL kinase inhibitor, results in lower mortality compared to standard of care (steroids with or without remdesivir) in hospitalised patients with COVID-19

Two randomised phase 2 studies: BGBC020 and ACCORD2

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Monday July 12th, 2021

12a. COVID-19 LB: Interventions for improving COVID outcome
Bemcentinib; two exploratory phase 2 COVID19 studies, distributed across 3 countries

<table>
<thead>
<tr>
<th>2020</th>
<th>2021</th>
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<tbody>
<tr>
<td>A M J</td>
<td>J A S</td>
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<tr>
<td>Bemcentinib</td>
<td>30</td>
</tr>
<tr>
<td>Standard of Care</td>
<td>34</td>
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</tbody>
</table>

Enrolment reopened
First patient
Last patient in

First patient
Last patient in

UK
WHO 9-point scale – graded increase in pulmonary support

- **Good health**: 0
- **Ill health**: 1
- **Death**: 8

<table>
<thead>
<tr>
<th>Level</th>
<th>Medical Intervention</th>
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<tbody>
<tr>
<td>0</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Worsening symptoms</td>
</tr>
<tr>
<td>2</td>
<td>Intubation and mechanical ventilation</td>
</tr>
<tr>
<td>3</td>
<td>OXYGEN</td>
</tr>
<tr>
<td>4</td>
<td>Non-invasive ventilation</td>
</tr>
<tr>
<td>5</td>
<td>Multi-organ failure I.C.U.</td>
</tr>
<tr>
<td>6</td>
<td>Intubation and mechanical ventilation</td>
</tr>
<tr>
<td>7</td>
<td>Outside hospital</td>
</tr>
<tr>
<td>8</td>
<td>Death</td>
</tr>
</tbody>
</table>

Time after infection

Time after hospitalisation

The vast majority of SARS-CoV2 infected patients recover from acute episode without need for hospital treatment.
Study Schematic - BGBC020 and ACCORD2 share identical design

* Bemcentinib treatment up to day 15. Discontinued earlier, if discharged or clinical improvement

COVID positive
N = 120

Admission to hospital

Viral load

Informed consent, Screen and Enrolment

SOC only

Bemcentinib + SOC

Loading Dose period
400mg once daily

ECG
PK

Maintenance: 200mg once daily

D1
D4
D5
D8
D11
D15

SOC only

Out-patient or remote

Out-patient or remote

Day 1
Day 15
Day 29
Day 60
Day 90

Study Participation

ECG*
P

400mg once daily

Viral load

(Day 29)
## Baseline patient characteristics and Safety

<table>
<thead>
<tr>
<th>Baseline WHO OCS</th>
<th>Bemcentinib</th>
<th>SOC</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Intent to use steroid</td>
<td>Bemcentinib</td>
<td>SOC</td>
<td>Total</td>
</tr>
<tr>
<td>3</td>
<td>N/A</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>No</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Yes</td>
<td>36</td>
<td>36</td>
<td>72</td>
</tr>
<tr>
<td>5</td>
<td>No</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>4</td>
<td>5</td>
<td>9</td>
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<tr>
<td>Total</td>
<td>58</td>
<td>57</td>
<td>115</td>
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</table>

<table>
<thead>
<tr>
<th>Baseline WHO OCS</th>
<th>ACCORD2</th>
<th>Bemcentinib</th>
<th>SOC</th>
<th>Total</th>
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<tbody>
<tr>
<td>Baseline Intent to use steroid</td>
<td>Bemcentinib</td>
<td>SOC</td>
<td>Total</td>
<td></td>
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<tr>
<td>3</td>
<td></td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>No</td>
<td>21</td>
<td>25</td>
<td>46</td>
</tr>
<tr>
<td>Yes</td>
<td>4</td>
<td>5</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>No</td>
<td>5</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>Yes</td>
<td>22</td>
<td>26</td>
<td>48</td>
<td></td>
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<tr>
<td>Total</td>
<td>29</td>
<td>33</td>
<td>62</td>
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<table>
<thead>
<tr>
<th>CRP</th>
<th>&gt;30mg/L</th>
<th>27</th>
<th>30</th>
<th>57</th>
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<tbody>
<tr>
<td>Proportion of patients</td>
<td>50%</td>
<td></td>
<td></td>
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</tbody>
</table>

### 5 Most Commonly reported Adverse Event (by PT)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Bemcentinib +SoC n=86</th>
<th>SoC n=89</th>
<th>Total N=175</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea</td>
<td>8 9</td>
<td>2 2</td>
<td>10 6</td>
</tr>
<tr>
<td>ALT increased</td>
<td>8 9</td>
<td>1 1</td>
<td>9 5</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>4 5</td>
<td>3 3</td>
<td>7 4</td>
</tr>
<tr>
<td>Headache</td>
<td>4 5</td>
<td>2 2</td>
<td>6 3</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1 1 5 6</td>
<td>6 3</td>
<td></td>
</tr>
</tbody>
</table>

4 patients discontinued bemcentinib due to adverse events (myocardial infarction - 1, raised ALT - 1, prolonged QTc - 1, septic shock and acute renal failure - 1)
1 interrupted bemcentinib due to diarrhoea

No SUSAR

IDMC review; no safety or tolerability signal of concern for further development in this COVID19 patient population.
Survival (day 29 after enrolment)

All participants

Max. duration of bemcentinib

Survival probability

Number at risk

Survival probability

Time

Survival probability

HR = 0.388 95% C.I. (0.103, 1.462)

WHO scores of 4 & 5 at baseline
AND screening CRP ≥ 30mg/L

HR = 0.306 95% C.I. (0.063, 1.472)

All-cause mortality
D29

Overall survival
D29

All patients

Grade 4 & 5 with CRP > 30mg/L

SoC

Bemcentinib

SoC

Bemcentinib

Max. duration of bemcentinib
Key Secondary endpoint – time to any worsening (incl death)

- Time to any worsening from starting grade, including death for any reason (measured up to day 29)

- Good health
- Ill health
- Death

Patient A
- Time after infection
- Time after hospitalisation

Patient B
- Non-invasive ventilation
- Intubation and mechanical ventilation

Patient C
- OXYGEN
- Multi-organ failure I.C.U.
Time to worsening by ≥1 grade in WHO score

All participants

HR = 0.679 95% C.I. (0.352, 1.309)

WHO scores of 4 & 5 at baseline AND screening CRP ≥ 30mg/L

HR = 0.310 95% C.I. (0.123, 0.781)

HR = 0.310 95% C.I. (0.123, 0.781)
Primary endpoint – time to improvement (recovery or discharge)

Time to improvement, earliest of either:
1. Time to discharge
2. time to 2-point improvement on WHO scale from baseline score
3. Time to “fit for discharge”

Good health

0

1

2

3

4

5

6

7

8

ill health

Death

Time after infection

Time after hospitalisation

Non-invasive ventilation

OXYGEN

Non-invasive ventilation

OXYGEN
Primary endpoint: time to recovery or discharge

All participants

HR = 1.318 95% C.I. (0.964, 1.802)

WHO scores of 4 & 5 at baseline
AND screening CRP ≥ 30mg/L

HR = 1.884 95% C.I. (1.236, 2.871)
AXL is targeted by enveloped viruses to enter cells and dampen the viral immune response

"apoptotic mimicry"
Enveloped viruses display phosphatidylserine, which is recognized by GAS6, the AXL receptor ligand, that mediates viral entry via endosomal pathway

Viral-mediated AXL receptor activation dampens type I interferon responses, key to cellular anti-viral defence mechanism
Bemcentinib acts on two host pathways prevents viral infection and promotes innate immunity

**Bemcentinib:**
- blocks AXL-dependent viral entry
- enhances anti-viral interferon response

**Key Features:**
- Orally bioavailable with PK supporting once-daily dosing
- Nanomolar in-vitro SARS-CoV2 potency
- Highly AXL selective (50 to 100-fold compared to TAM kinase family)
- Favourable safety & tolerability (oncology programmes >400 patients dosed)
Bemcentinib - inhibits SARS-CoV2 in human lung epithelial cell lines

paired SARS2 N / GAPDH ddCt

normalized to Virus only WA-1

[bemcentinib] – 0.1 µm, 0.33 µm, 1.0µm

Virus Only
1 µM Bem
Clinical evidence supporting antiviral mechanism of action
Exploratory endpoint – viral kinetics in saliva

<table>
<thead>
<tr>
<th>Time after first dose</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>7</th>
<th>10</th>
<th>14</th>
<th>28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bemcentinib (n)</td>
<td>53</td>
<td>48</td>
<td>40</td>
<td>32</td>
<td>14</td>
<td>33</td>
<td>37</td>
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<tr>
<td>SoC (n)</td>
<td>49</td>
<td>43</td>
<td>26</td>
<td>25</td>
<td>16</td>
<td>22</td>
<td>35</td>
</tr>
</tbody>
</table>
Clinical evidence supporting antiviral mechanism of action

Exploratory endpoint – viral kinetics in saliva

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<th>7</th>
<th>10</th>
<th>14</th>
<th>28</th>
</tr>
</thead>
<tbody>
<tr>
<td>bemcentinib - no antiviral (n)</td>
<td>25</td>
<td>24</td>
<td>13</td>
<td>17</td>
<td>3</td>
<td>16</td>
<td>20</td>
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<tr>
<td>bemcentinib + antiviral (n)</td>
<td>28</td>
<td>24</td>
<td>27</td>
<td>15</td>
<td>11</td>
<td>16</td>
<td>17</td>
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<tr>
<td>SoC - no antiviral (n)</td>
<td>19</td>
<td>16</td>
<td>8</td>
<td>9</td>
<td>5</td>
<td>10</td>
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<td>18</td>
<td>16</td>
<td>11</td>
<td>12</td>
<td>22</td>
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</tbody>
</table>
**Summary**

In **hospitalised** patients, **requiring oxygen** but not intubated across a diverse range of healthcare scenarios in three continents

When added to corticosteroid based standard-of-care therapy, a finite course of daily oral therapy with bemcentinib:

Showed evidence for therapeutic benefit on meaningful clinical endpoints

- **Survival** to day 29 - 96.6% vs 91.2% with SoC alone
- Reduced likelihood of progression of pulmonary distress to require ventilation — 69% lower than SoC in higher severity cohort
- Increased likelihood of shorter time to recovery or discharge — 88% greater than SoC in higher severity cohort

Clinical data adds support to pre-clinical evidence for bemcentinib - host-targeted anti-viral mechanism of action on SARS-CoV2:

- Impairing viral cell entry
- Enhancing innate type-1 IFN immune response to virus

This signal of therapeutic benefit, requires confirmation in a prospectively designed placebo RCT — magnitude of effect indicates the requisite study population for statistical power, would likely be of modest size.
Acknowledgements

All participating patients in South Africa, India and UK

Investigator and study site staff

<table>
<thead>
<tr>
<th>South Africa</th>
<th>India</th>
<th>UK</th>
</tr>
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<tbody>
<tr>
<td>Dr van Zyl</td>
<td>Dr Joshi</td>
<td>Prof Wilkinson</td>
</tr>
<tr>
<td>Dr Engelbrecht</td>
<td>Dr Pereira</td>
<td>Dr Horsley</td>
</tr>
<tr>
<td>Dr Basson</td>
<td>Dr Sahu</td>
<td>Prof Ryder</td>
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<tr>
<td>Dr Siebert</td>
<td>Dr Kumar</td>
<td>Dr Crooks</td>
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<tr>
<td>Dr Hussen</td>
<td>Dr Sutariya</td>
<td>All ACCORD platform</td>
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<td>investigators</td>
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