Letermovir - from Bench to Bedside: Development of a Novel Drug Against Cytomegalovirus

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Human Cytomegalovirus (HCMV) Infections

- In immuno-incompetent hosts, HCMV causes life-threatening disease and increases morbidity and mortality

Patient populations

- Organ transplant recipients
  - Solid Organ transplant (SOT)
  - Bone Marrow transplant (BMT)

- Newborns
  (pre-, peri-, postnatal infection)

- AIDS patients

- Leukemia

Examples for disease manifestations

<table>
<thead>
<tr>
<th>Disease Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colitis, hepatitis, encephalitis, sepsis, HCMV pneumonia</td>
</tr>
<tr>
<td>Neurologic impairment, hepatic/splenic illness, hearing loss, death</td>
</tr>
<tr>
<td>Retinitis, encephalitis, colitis, pneumonitis</td>
</tr>
<tr>
<td>Lymphomatosis, hepatitis</td>
</tr>
</tbody>
</table>

Medical need high and rising by increasing numbers of immuno-incompetent patients

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Marketed drugs address invariably the same target: The polymerase of HCMV

### VALCYTE®
Valganciclovir  
ROCHE, Launch 2001

### Cymeven®
Ganciclovir  
ROCHE / SYNTEX, Launch 1988

### VISTIDIE®
Cidofovir  
GILEAD, Launch 1997  
(IV only; dose-limiting nephrotox)

### FOSCAVIR®
Foscarnet  
ASTRA ZENECA, Launch 1995

<table>
<thead>
<tr>
<th><strong>Limitations of all marketed drugs</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>- <strong>Significant side-effects</strong> (kidney tox, bone marrow tox, mutagenic, carcinogenic, teratogenic potential)</td>
</tr>
<tr>
<td>- Limited duration of treatment</td>
</tr>
<tr>
<td>- Limited higher doses in acute cases</td>
</tr>
<tr>
<td>- Limited use in prophylaxis</td>
</tr>
<tr>
<td>- No use in HCMV-infected newborns</td>
</tr>
<tr>
<td>- No use in pregnant women with active HCMV disease</td>
</tr>
<tr>
<td>- <strong>Increasing Cross-resistance</strong></td>
</tr>
<tr>
<td>- Valtrex is well tolerated but less efficacious for HCMV</td>
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</tbody>
</table>

There is an urgent need for better drugs

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Letermovir – Chemistry

SAR summary

Lipophilic and polar substituents well tolerated in 6- and 8-Position; pyridyls show no improvement; improvement through bis-substitution

Lipophilic substituent's gave most active compounds: 3-position > 4-position > 2-position; no improvement of activity through bis-substitution; benzyl-type substituents not tolerated

Replacement with ethylenediamines, piperidines, cyclohexyl and phenyl results in loss of activity

Substitution in 3- and 4-position well tolerated
**Letermovir – Nonclinical data**

Mode of action: Targeting a viral process

*In presence of Letermovir*

→ no correct cleavage/packaging of HCMV progeny DNA
→ no production of infectious particles

**No mechanism-based side effects**

No activation by viral enzyme necessary – protective to uninfected cells
No cross resistance to existing drugs
**Letermovir – Nonclinical data**

Nanomolar antiviral activity *in vitro*

- steep dose-response curve
- surpasses the current standard-of-care Ganciclovir
- favorable selectivity index (SI)

**Ganciclovir**

- $EC_{50}$: 2.0 µM
- $EC_{90}$: 14.5 µM
- $CC_{50}$: >333 µM
- SI: >174

**Letermovir**

- $EC_{50}$: 4.5 nM
- $EC_{90}$: 6.1 nM
- $CC_{50}$: ~90 µM
- SI: ~18,000

Letermovir is approx. 500-fold superior to Ganciclovir *in vitro*
**Letermovir – Nonclinical data**

*In vitro* ability to suppress high viral loads

<table>
<thead>
<tr>
<th>MOI</th>
<th>Letermovir EC₅₀ [µM]</th>
<th>Ganciclovir</th>
<th>Maribavir</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.003</td>
<td>0.0013</td>
<td>0.99</td>
<td>0.29</td>
</tr>
<tr>
<td>0.01</td>
<td>0.0015</td>
<td>0.68</td>
<td>0.17</td>
</tr>
<tr>
<td>0.03</td>
<td>0.0029</td>
<td>1.74</td>
<td>0.38</td>
</tr>
<tr>
<td>0.1</td>
<td>0.0034</td>
<td>2.21</td>
<td>0.94</td>
</tr>
<tr>
<td>0.3</td>
<td>0.0036</td>
<td>6.51</td>
<td>no activity</td>
</tr>
<tr>
<td>1</td>
<td>0.0042</td>
<td>5.26</td>
<td>no activity</td>
</tr>
</tbody>
</table>

- Letermovir EC₅₀ increases by a factor of 3 upon ~333 fold increase of virus titer
- Ganciclovir EC₅₀ increases by a factor of ≥5
- Maribavir lacks sufficient potency to combat high MOI infections in cell culture

**Low MOI dependency seen with Letermovir**
**Letermovir – Phase 1 program**

Overview of completed trials

- 2 Single Dose escalation trials (oral)
  - up to 320 mg
- 2 Multiple Dose escalation trials (oral)
  - up to 240 mg BID
- 1 food interaction trial (oral)
- 1 Mass balance / Met ID trial (oral)
- 1 relative bioavailability trial (new tablet, oral)
- Drug-drug interaction with Cyclosporine A (oral)
- Drug-drug interaction with Tacrolimus (oral)
- Drug-drug interaction with Midazolam (oral)
- Renal impairment
- Liver impairment
- Iv dosing
**Letermovir – Phase 1 program**

**Summary of PK and Safety**

- **PK after oral dosing (general)**
  - $T_{\text{max}}$ about 1.5 h
  - Terminal half-life about 10 h
  - Elimination mainly unchanged via feces (biliary)

- **Safety in healthy volunteers**
  - >300 healthy volunteers (males and females)
  - No clinically relevant drug-related AEs observed over the dosing regimes studies
  - No exposure related safety issues
  - No influence on vital signs and ECG parameters

**Letermovir is safe and well-tolerated, OD dosing is feasible**
Letermovir – Phase 2a preemptive treatment
Trial Design AIC001-2-001 (proof-of-concept)

- Randomized, controlled, open-label, multi-center
- HCMV pre-emptive treatment trial
  - Primary endpoint – Decline of HCMV DNA from baseline on day 15
  - Secondary endpoints – Safety, tolerability, PK, further efficacy
- 14 days treatment, 3 treatment groups (randomisation 1:1:1)
  - Letermovir 40 mg BID
  - Letermovir 80 mg OD
  - OC (local standard of care: VGCV)
- 27 Transplant patients (kidney, kidney/pancreas, bone marrow)
  - positive HCMV viremia at any level
  - eligible for preemptive therapy

Goal: Proof-of-concept for antiviral efficacy of Letermovir
Letermovir – Phase 2a preemptive treatment

Summary

- Safety and PK of Letermovir
  - Safe and well tolerated
  - No need for major adjustment of immunosuppressive co-medications
  - Comparable pre-dose levels with 40 mg BID and 80 mg OD
  - OD dosing possible
  - Mean trough-levels in all patients consistently higher than EC$_{90}$

- Efficacy
  - No patient developed HCMV disease under therapy
  - Comparable to VGCV
  - Successful treatment of patients infected with multi-resistant or VGCV-resistant strains

Proof-of-Concept for antiviral activity of Letermovir
**Letermovir – Phase 2a preemptive treatment**

**Efficacy – Primary endpoint 'Reduction of viral load'**

Individual HCMV-DNA load change from baseline to Day 15 (log10 copies/mL at central laboratory)

**Subgroup analyses**

<table>
<thead>
<tr>
<th>PP Population (N=25)</th>
<th>Patients with baseline viremia at any level (N=19)</th>
<th>Patients with baseline viremia ≥4 log10 copies/mL (N=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40mg BID (N=7)</td>
<td>40mg BID (N=4)</td>
<td>40mg BID (N=1)</td>
</tr>
<tr>
<td>80mg QD (N=9)</td>
<td>80mg QD (N=8)</td>
<td>80mg QD (N=4)</td>
</tr>
<tr>
<td>OC (N=9)</td>
<td>OC (N=7)</td>
<td>OC (N=5)</td>
</tr>
</tbody>
</table>

**POC reached:** Statistically significant decrease vs. baseline

No statistically significant differences between treatment groups

★ p <0.05 vs. baseline
**Letermovir – Multiresistant HCMV**

**Case report 1: Patient from Phase 2a with HCMV viremia**

Patient history:
- Kidney / pancreas transplanted patient (D+/R-)
- Treatment with GCV and FOS failed
- Resistance Phenotype: GCV, CDV, FOS
- Treatment with Letermovir 80 mg OD for 14 days:
  - Full resolution of HCMV viremia

**Successful treatment of multiresistant HCMV in the clinic**
**Letermovir – Multiresistant HCMV**

**Case report 1: Patient from Phase 2a with HCMV viremia**

- Treatment with ganciclovir and foscarnet failed
  80 mg AIC246 once daily for 14 days

(Central lab CMV DNA PCR)

Successful treatment of multiresistant HCMV in the clinic
Letermovir – Multiresistant HCMV disease

Case report 2: EIND patient with multi-organ disease

Patient history:

- Bilateral lung transplant for cystic fibrosis (D+/R+)
- Development of HCMV pneumonitis under VGCV prophylaxis, clinical and virological progression despite treatment with VGCV, foscarnet, leflunomide, cidofovir, HCMV hyperimmune globulin, an artemisinin derivative and a lipid conjugate of cidofovir (CMX001)
  - HCMV pneumonitis, colitis, retinitis
- Resistance phenotype: Ganciclovir, Foscarnet, Cidofovir

Treatment with Letermovir under emergency IND for 49 days

- Viremia resolved on Day 28
- Resolution of pneumonitis, retinitis and colitis
- No virological relapse up to 4 months after cessation of therapy
- Proof of efficacy in difficult to treat condition
Letermovir – Multiresistant HCMV
Case Report 2: Radiological resolution of CMV pneumonia

CT chest

14May2010

10Jun2010

Hazy, patchy, and ill-defined nodular opacities seen in the lung as signs of pneumonia
Letermovir – Multiresistant HCMV
Case Report 2: Resolution of CMV disease

Colonoscopy before and after treatment
**Letermovir – prophylaxis for blood precursor cell recipients**

Phase II Dose-ranging trial design:

Weekly testing for HCMV replication by scheduled visits (PCR and/or antigenemia)

- **HBPC transplantation** (within 40 days before randomisation)
- **84 days treatment**
  - 60 – 120 – 240 mg vs. placebo
  - once daily
- **7 days follow-up**

- 132 allogeneic human blood cell precursor (HBCP) recipients
- Randomisation 1:1:1:1 → 33 patients in each Letermovir and placebo groups
- Main inclusion criteria:
  - HCMV seropositivity within 1 year before transplantation
  - First allogeneic HBCP transplantation within 40 days before randomisation due to e.g. leukemia, lymphoma, multiple myeloma
  - No active HCMV replication detectable within 5 days before trial start
The ‘Failure’ of HCMV prophylaxis includes

- Patients who developed systemic detectable HCMV Replication, and/or an HCMV End-Organ disease, i.e. ‘true failure’ of HCMV prophylaxis

and

- Patients who discontinued trial medication prior to Day 84 due to any other reason (e.g. death, adverse event, consent withdrawn, non-compliance)
Incidence of HCMV Prophylaxis Failure within the 84-day Treatment Period (FAS)

![Bar chart showing incidence of HCMV prophylaxis failure across different dosages of the drug.]

- **Placebo**: 36 cases, 0 failures, 27 other discontinuations.
- **60 mg qd**: 52 cases, 27 failures, 21 other discontinuations.
- **120 mg qd**: 68 cases, 13 failures, 19 other discontinuations.
- **240 mg qd**: 71 cases, 24 failures, 6 other discontinuations.

Legend:
- Red: True HCMV prophylaxis failure
- Light yellow: Other discontinuations
- Light green: No failure
Incidence of HCMV Prophylaxis Failure within the 84-day Treatment Period (FAS)

Subgroup Analysis: Exclusion of individuals with positive HCMV DNA count on day 1

<table>
<thead>
<tr>
<th>N (%) patients</th>
<th>Letermovir 60 mg qd N = 33</th>
<th>Letermovir 120 mg qd N = 31</th>
<th>Letermovir 240 mg qd N = 34</th>
<th>Placebo N = 33</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCMV prophylaxis failure</td>
<td>7 (21)</td>
<td>6 (19)</td>
<td>2 (6)</td>
<td>12 (36)</td>
</tr>
<tr>
<td>HCMV prophylaxis failure with HCMV DNA on day 1</td>
<td>2 (6)</td>
<td>4 (13)</td>
<td>2 (6)</td>
<td>3 (11)</td>
</tr>
<tr>
<td>„True“ HCMV prophylaxis failure</td>
<td>5 (15)</td>
<td>2 (6)</td>
<td>0 (0)</td>
<td>9 (27)</td>
</tr>
</tbody>
</table>

No HCMV prophylaxis failure with Letermovir 240 mg once daily when excluding patients with active HCMV replication at day 1

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Time to Onset of HCMV Prophylaxis Failure within the 84-day Treatment Period (FAS)

Highly significantly different with Letermovir 240 mg once daily (p value: 0.002 versus placebo)

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Clinical Laboratory Safety, Vital Signs and ECGs

<table>
<thead>
<tr>
<th>N (%) Patients with at least one predefined change post baseline</th>
<th>Letermovir 60 mg qd N = 33</th>
<th>Letermovir 120 mg qd N = 31</th>
<th>Letermovir 240 mg qd N = 34</th>
<th>Placebo N = 33</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin: PC = -2 g/dL</td>
<td>10 (30)</td>
<td>11 (35.5)</td>
<td>8 (23.5)</td>
<td>7 (21)</td>
</tr>
<tr>
<td>WBC: PC = -2000 /mm3</td>
<td>11 (33)</td>
<td>13 (42)</td>
<td>10 (29)</td>
<td>9 (27)</td>
</tr>
<tr>
<td>Eosinophils: PC = +20 %</td>
<td>2 (6)</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Neutrophils: PC = -20 %</td>
<td>9 (27)</td>
<td>9 (29)</td>
<td>6 (18)</td>
<td>10 (30)</td>
</tr>
<tr>
<td>Platelets: PC = -100,000 /mm3</td>
<td>4 (12)</td>
<td>0</td>
<td>6 (18)</td>
<td>4 (12)</td>
</tr>
</tbody>
</table>

- Clinical Laboratory safety: comparable between Letermovir and placebo
- Vital signs: no major findings in shifts from baseline and no statistically significant incidences of predefined change abnormalities between Letermovir and placebo groups
- ECGs: no major findings in central ECGs reading

Overall good safety profile of Letermovir
# TEAEs Leading to Permanent Trial Medication Discontinuation (Safety Set)

<table>
<thead>
<tr>
<th>&gt; 5% Patients with any TEAE in any treatment group by SOC, PT</th>
<th>Letermovir 60 mg qd N = 33</th>
<th>Letermovir 120 mg qd N = 31</th>
<th>Letermovir 240 mg qd N = 34</th>
<th>Placebo N = 33</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N (%) Pts with any TEAE [events] leading to TM discontinuation</strong></td>
<td>9 (27) [17]</td>
<td>9 (29) [10]</td>
<td>7 (21) [7]</td>
<td>19 (58) [26]</td>
</tr>
<tr>
<td>CMV infection/viremia</td>
<td>5</td>
<td>6</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Immune System disorders</td>
<td>2 (6) [2]</td>
<td>0</td>
<td>1 (3) [1]</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>1 (3) [2]</td>
<td>0</td>
<td>1 (3) [1]</td>
<td>3 (9) [4]</td>
</tr>
<tr>
<td>Blood &amp; Lymphatic system disorders</td>
<td>0</td>
<td>1 (3) [1]</td>
<td>0</td>
<td>2 (6) [2]</td>
</tr>
<tr>
<td>General disorders &amp; Admin. Site conditions</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (6) [3]</td>
</tr>
</tbody>
</table>

Overall, up to ~40% less discontinuation of Letermovir due to TEAE(s) When excluding CMV infections, similar profile to placebo
“It becomes obvious that this drug with its novel mechanism of action offers clear benefits over existing therapies.”
Prof. Gerhard Ehninger, University Hospital Dresden, Germany, coordinating investigator for German trial arm

“The safety data certainly look very good. There is no distressing signal for any significant toxicity in any of the Letermovir dose groups”
Prof. Per Ljungman, Karolinska University Hospital, Sweden
Chairman of Safety Monitoring Committee for the Phase 2b trial

“This study shows that Letermovir is a safe, effective treatment to prevent these infections. This is a major advance for the care of these immunocompromised patients.”
Prof. Richard Champlin, Director of the Bone Marrow Transplantation Center, Houston, Texas
AiCuris & Merck Contract 2012: Merck takes over development

Downpayment 110 mio €
Milestones 332,5 mio €
Royalties on worldwide sales
Acknowledgements Letermovir

- **Phase 2A treatment**


- **Phase 2B prophylaxis**


- **University of Erlangen viral testing**

  M. Marschall, T. Stamminger

- **AiCuris**


- **We are grateful for the excellent contributions of the chemists from Bayer:**

- **All trial participants**
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