CMV antiviral drug development – a European regulatory perspective

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DISCLAIMER

- **These slides present Filip Josephson's interpretation of the state of affairs and may ultimately not coincide with EMA/CHMP policy**

The surrogacy of CMV viremia is accepted

- **A demonstration of antiviral efficacy principally suffices to infer clinical benefit; although data on relevant clinical outcomes should be collected, there is no need for a *formal efficacy demonstration* on clinical endpoints within a drug development program.**
- **All regulatory approval is based on positive benefit/risk *balance* within the scope of the labelled indication when the drug is used as specified in the product information.**
- **Therefore the applicant needs to justify the claimed relation of the demonstrated antiviral efficacy and clinical benefits in quantitative terms, based on available science, and how the inferred clinical benefit *outweighs* relevant safety concerns within the proposed indication and conditions for use**

Consequences of the acceptance of the surrogacy of CMV viremia. PK/PD

- **The core of the efficacy demonstration is the description of the PK/PD relation; i.e. the quantitative relation of drug exposure to the inhibition of viral replication *and* to the durability of virological response (prevention of treatment-emergent resistant variants)**
- **Study settings with quantifiable viremia are substantially more informative than prophylaxis settings: *what are appropriate settings and designs for informative studies on the PK/PD relation of a new antiviral*?**
- **Bridging: for a new agent, *comparative viral kinetic data versus GCV/vGCV* in different scenarios may be of particular value**
- **Viral kinetics in retreatment of recurrent quantifiable viremia may be further informative of barrier to resistance / durability of response**
- ***How should potential combination therapy be explored*?**

Consequences cont:d. Extrapolation

- **Extrapolation of efficacy and positive B/R beyond the studied scenario(s) is *principally possible*, but dependent on the understanding of the PK/PD relation of the drug.**
- **The appropriateness of the proposed treatment strategy (dosing regimen, treatment duration, potential need combination therapy etc) needs to be justified in the non-studied treatment scenario.**
- ***How does the clinical setting and patient characteristics (e.g., HSCT versus various SOT , immune status / immunosuppressive regimen, prophylaxis versus preemptive etc) impact pharmacokinetics and/or the sum antiviral drug pressure required for clinical benefit?***
- **There should be no safety concerns particular to the non-studied scenario that would imply potentially negative B/R**

Further aspects

- **No CHMP guideline on CMV drug development is presently drafted, in the absence of a modern ”successful example”; sponsors are strongly encouraged to discuss their development plans with European regulators through ”central” scientific advice (i.e. via the EMA)**
- **Consider combined regulatory / HTA advice**
- **Format of labelled indications for new drugs (e.g. ”narrow” versus ”broad”) remains to be decided based on emerging data and treatment paradigm**