using expressed enzyme (Biron *et al.*, 2002; Shannon-Lowe and Emery, 2010). In the absence of functioning *UL97* kinase, whether as a result of a gene knockout or inhibition by maribavir, viral replication is severely impaired, with an abnormal cell culture cytopathic effect characterized by the nuclear aggregation of excess amorphous viral proteins, including the tegument protein pp65 (Prichard *et al.*, 2005; Prichard, 2009). Impaired *UL97* function appears to cause a defect in viral encapsidation (Wolf *et al.*, 2001) and/or egress of viral particles from the nucleus (Krosky *et al.*, 2003a). In addition, viral DNA synthesis may also be reduced (Wolf *et al.*, 2001; Biron *et al.*, 2002). CMV replication is not completely shut off in the absence of the *UL97* kinase; the widely varying maribavir EC_{50} values under different assay conditions suggest that host cells can variably substitute for the normal function of *UL97*.

The CMV *UL97* kinase phosphorylates many host cell and viral substrates (Oberstein *et al.*, 2015). For example, it can phosphorylate the cell cycle regulator Rb (mimicking the action of cyclin-dependent kinases) (Hume *et al.*, 2008); nuclear lamin proteins and viral nuclear egress components encoded by *UL50* and *UL53* (Milbradt *et al.*, 2010; Sharma *et al.*, 2015); and viral proteins encoded by genes *UL44* (Krosky *et al.*, 2003b; Marschall *et al.*, 2003), *UL69* (Thomas *et al.*, 2009), *UL83* (Becke *et al.*, 2010), and *UL97* (autophosphorylation) (He *et al.*, 1997), among others. The relative importance of the various phosphorylation targets to overall *UL97* biological function remains ill-defined.

The exact mechanism of action of maribavir against EBV is unresolved. In treated cell cultures, maribavir inhibits the phosphorylation of the viral protein EA-D, a processivity factor for the viral DNA polymerase (Zacny *et al.*, 1999; Wang *et al.*, 2009). However, maribavir did not directly inhibit the EBV kinase BGLF4, which is capable of phosphorylating EA-D, when assayed using plasmid expression vectors (Gershburg and Pagano, 2002) or by autophosphorylation of the purified enzyme (Gershburg *et al.*, 2004). In Akata cells, maribavir treatment resulted in widespread reduction of EBV transcripts, especially a subset of gamma transcripts (Wang *et al.*, 2009), an effect that is also observed with BGLF4 knockout virus (Whitehurst *et al.*, 2013), suggesting that maribavir action is somehow linked to BGLF4 inhibition and/or its downstream effects.

4. MODE OF DRUG ADMINISTRATION AND DOSAGE

4a. Adults

Maribavir has been administered in clinical trials as an oral tablet only. Phase I clinical trials included a wide range of single doses from 50 to 1600 mg (Wang *et al.*, 2003) and daily doses up to 2400 mg (Lalezari *et al.*, 2002). After a phase II trial, it was concluded that low doses of 100 mg twice daily were suitable for prophylaxis (Winston *et al.*, 2008), but phase III trials conducted using this dosage were unsuccessful (Marty *et al.*, 2011; Winston *et al.*, 2012). Subsequent phase II treatment trials used much higher doses of 400 to 1200 mg twice daily.

4b. Newborn infants and children

There are no available data on the administration of maribavir in infants and children.

4c. Pregnant and lactating mothers

There are no data available on the use of maribavir in pregnant and lactating mothers.

4d. Those requiring altered dosages

PATIENTS WITH IMPAIRED RENAL FUNCTION

The pharmacokinetics of maribavir have been studied in subjects with varying degrees of renal impairment (Swan *et al.*, 2007), including creatinine clearances as low as 12 ml/minute, but excluding those undergoing dialysis. Because the pharmacokinetics of unmetabolized maribavir (maximum concentration [C_{max}], area-under-the-concentration-time curve [AUC], half-life [$t_{½}$]) were little affected by renal function, no dose adjustment was deemed necessary within the range of renal function studied. There was some accumulation of the pharmacologically inactive *N*-dealkylated metabolite, of undetermined clinical significance.

PATIENTS WITH IMPAIRED HEPATIC FUNCTION AND THE ELDERLY

No guidelines for dose adjustment have been published for patients with impaired hepatic function or for the elderly.

5. PHARMACOKINETICS AND PHARMACODYNAMICS

5a. Bioavailability

After oral administration, maribavir is rapidly absorbed to reach peak plasma concentrations within 1–3 hours; at least 30–40% of the dose is absorbed as judged by the amount of metabolites recovered in the urine (Lalezari *et al.*, 2002; Wang *et al.*, 2003). Over a dose range of 100–1600 mg, the C_{max} of maribavir increases slightly less than proportionally to the dose and the AUC increases slightly more than proportionally to the dose (Wang *et al.*, 2003). With a 100-mg dose, the single-dose C_{max} in healthy individuals was 3.3 μg/ml (8.8 μM) and after 12 hours, the plasma concentration was ~ 10% of the C_{max} (Wang *et al.*, 2003). In a phase III trial using 100 mg twice daily, the C_{max} was 5.8 ± 3.1 μg/ml and C_{min} was 1.9 ± 1.6 μg/ml after 4 weeks (Marty *et al.*, 2011). Maribavir is cleared from the plasma with a $t_{½}$ of 3–5 hours. It is highly (98%) protein bound (Koszalka *et al.*, 2002). Administration with a high-fat meal delayed the time to maximal drug concentration by about 2 hours and decreased the C_{max} by about 30%.

5b. Drug distribution

No human data have been published on the distribution of maribavir to sites such as cerebrospinal fluid (CSF), eye,