of neutropenia between placebo and any dose of maribavir) and lack of nephrotoxicity.

There are no human data on the safety of maribavir in pregnancy, for either the mother or the fetus.

7. CLINICAL USES OF THE DRUG

As of early 2017, maribavir is an experimental drug with no US Food and Drug Administration (FDA) approved indications. Although the low-dose phase III CMV prevention trials failed, new phase III CMV treatment trials are being conducted to follow up on positive findings of recently completed phase II treatment trials.

7a. Cytomegalovirus infection

ASYMPTOMATIC VIRAL SHEDDING

A phase I trial studied the antiviral effect of a 1-month course of maribavir at doses from 400 to 1200 mg/day in HIV-infected adult males with asymptomatic CMV shedding in urine and semen (Lalezari *et al.*, 2002). The study showed that maribavir markedly decreased the asymptomatic shedding of CMV and that this effect appeared to be largely unrelated to dose. Maribavir was given at doses of 100, 200, or 400 mg three times daily, or 600 mg twice daily, with between five and seven HIV-infected subjects per group. Results at the end of the 28-day drug administration, compared with pretreatment data, showed a mean decrease of 3.7 log in semen CMV infectivity (plaque count) among those receiving 200 or 400 mg three times daily, a 2.9-log decrease with 100 mg three times daily, and a 3.3-log decrease with 600 mg twice daily.

A randomized, dose-ranging phase II trial in transplant recipients was conducted in several European countries in 2012–2014 to compare the anti-CMV activity of three doses of maribavir (400, 800, and 1200 mg) twice daily with that of valganciclovir for the treatment of CMV infection without end-organ disease (EU Clinical Trials register 2010-024247-32). Pending publication of results, a regulatory filing from the sponsor (Shire, 2015) stated that "maribavir, at all doses, was at least as effective as valganciclovir in the reduction of circulating CMV to below the limits of assay detection." Preliminary data have been presented (Maertens *et al.*, 2016) and a corresponding phase III trial is planned for launch in 2017.

PREVENTION OF CMV INFECTION AFTER STEM CELL AND SOLID ORGAN TRANSPLANTATION

A phase II safety, tolerability, and antiviral activity study of oral maribavir in CMV-seropositive adult allogeneic stem cell transplant recipients was conducted as a multicenter, randomized, double-blind, placebo-controlled, dose-ranging study and was reported as successful (Winston *et al.*, 2008). Patients were enrolled upon successful stem cell engraftment, had no detectable CMV infection (by pp65 antigenemia or plasma polymerase chain reaction [PCR] for CMV DNA) at baseline, and were not receiving any other anti-CMV therapy. Patients were randomized to placebo or maribavir doses of 100 or 400 mg twice daily or 400 mg once daily and scheduled for up to 12 weeks of treatment. Weekly CMV surveillance was done by testing for pp65 antigenemia or plasma CMV DNA and, if positive, the study drug was stopped and standard CMV therapy (usually ganciclovir) was started. Each study group had 26–28 subjects. At the lowest dose of 100 mg, the incidence of CMV infection within 100 days after transplant was 39% with placebo and 15% with maribavir (when assessed by pp65 antigenemia), or 46% with placebo and 7% with maribavir (when assessed by detection of plasma CMV DNA). Use of standard anti-CMV therapy was reduced from 57% with placebo to 15% with maribavir. All of these differences reached statistical significance. There were three cases of CMV end-organ disease among placebo recipients and none among maribavir recipients, but the difference did not reach statistical significance. The lowest dose of maribavir (100 mg twice daily), appeared to be as effective as the higher doses tested.

Two phase III trials were then completed at the 100 mg twice daily dose for CMV prophylaxis in stem cell recipients and in liver transplant recipients; both were unsuccessful. The study in stem cell recipients (Marty *et al.*, 2011) enrolled 681 subjects randomized 2:1 to maribavir or placebo, where either the donor or recipient was CMV seropositive. Study drug administration and virologic monitoring were similar to the phase II trial just discussed. The primary end point was the incidence of CMV disease at 6 months (about 3 months beyond the intended period of prophylaxis); by this criterion there was no difference between recipients of maribavir (4.4%) or placebo (4.8%). Because any subjects with viral breakthrough on study drug could be given standard therapy to prevent CMV disease, such interim treatment probably had a strong effect on the primary end point comparison. However, the trial failed to confirm the phase II findings of a significant reduction in use of standard therapy or incidence of infection as detected by plasma CMV DNA, although there was a reduced incidence of pp65 antigenemia at 100 days (26% with maribavir vs. 35% with placebo; $p = 0.02$). The negative results were corroborated by a contemporaneous phase II trial in 303 liver transplant recipients randomized to prophylaxis with maribavir or oral ganciclovir (1000 mg three times daily) (Winston *et al.*, 2012). Using the primary end point of incidence of CMV disease at 6 months, noninferiority of maribavir (12%) compared with oral ganciclovir (8%) could not be established. When assessed at 100 days, whether by incidence of CMV disease, detection of CMV DNA by PCR or antigenemia, or use of standard therapy, maribavir was definitively worse ($p < 0.001$) than oral ganciclovir as prophylaxis. Although the low dose used in the prophylaxis trials has been criticized (Snydman, 2011), no further prophylaxis trials using higher doses have been initiated.

TREATMENT OF CMV INFECTION UNRESPONSIVE TO EXISTING ANTIVIRALS

Because of its distinct antiviral mechanism, there is strong interest in the role of maribavir in treating active CMV infection