cidofovir-treated animals. Antiviral treatment also reduced mortality. In placebo-treated animals, mortality was 7/8 (87.5%). In the cidofovir group, mortality was 0/8 animals, compared to 3/8 (38%) animals in the gefitinib group. By qPCR, cidofovir therapy prevented DNAemia; gefitinib-treated animals had significantly lower viral loads than controls. In summary, gefitinib had in vitro activity against GPCMV and in vivo animals treated with gefitinib had improved weights and trends toward reduced mortality and reduced magnitude of DNAemia. These results derived from this initial trial support further evaluation of the potential for gefitinib as an anti-CMV antiviral in the guinea pig model.

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20

Successful Treatment in the Monkeypox and Variola Primate Models of Smallpox by the Oral Drug ST-246

John Huggins[1,*], Arthur Goff[1], Mucker Eric[1], Nancy Twenhafel[1], Jennifer Chapman[1], Mallory Tate[2], Rob Jordan[3], Tove' Bolken[3], Dennis Hruby[3]

[1] US Army Medical Research Institute of Infectious Diseases; [2] Centers for Disease Control and Prevention; [3] Siga Technologies Inc.

Based on activity in multiple small animal models, oral ST-246 was evaluated in our variola virus-cynomolgus monkey model of classical smallpox, which closely resembles human disease. The placebo group demonstrated typical disease with >1250 pox lesions and 33% mortality. Oral gavage with ST-246 begun 24 h after infection, when bone marrow, spleen, some lymph nodes and liver had $>10^8$ genomes/g and all tissues had 10^4–10^6 g^{-1}, eliminated disease as judged by complete lack of lesion formation, the best predictor of smallpox disease severity in humans, with no significant clinical or laboratory findings. Virus levels in blood did not increase over pretreatment levels (10^6 mL^{-1}) and was cleared in 6 days versus 16 days for placebo based on historical data. ST-246 was next evaluated using our monkeypox virus-cynomolgus monkey model of classical smallpox, which also closely resembles human disease. The placebo-treated group demonstrated typical disease with >1500 pox lesions and 100% mortality. Oral gavage treatment with ST-246 begun 1 day after infection, when bone marrow, spleen, some lymph nodes and liver had $>10^7$ genomes/g and all tissues have 10^5–10^6 g^{-1}, eliminated disease as judged by complete lack of lesion formation, with no significant clinical or laboratory findings. Virus levels in blood did not increase over pretreatment levels and was cleared in 4 days versus 16 days for placebo or IV Cidofovir™ based on historical data. Oral gavage treatment with ST-246 begun 3 days after infection, when bone marrow, spleen, some lymph nodes and liver had $>10^8$ genomes/g and all tissues had $>10^6$ g^{-1}, eliminated disease as judged by complete lack of lesion formation in 2/3 monkeys and <5% of control lesions in 1/3 that did not progress, with no significant clinical or laboratory findings. Virus levels in blood did not increase over pretreatment levels and was cleared in 6 days versus 16 days for placebo. ST-246 has been granted fast-track IND status and has not shown toxicity in phase I human single oral dosing at 2000 mg.

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Oral Session IV: Hepatitis Viruses I

21

Design and Characterization of R1626, A Prodrug of the HCV Replication Inhibitor R1479 (4′-Azidocytidine) With Enhanced Oral Bioavailability

Klaus Klumpp[1,*], David Smith[1], Michael Brandl[1], Tom Alfredson[1], Keshab Sarma[1], Mark Smith[1], Isabel Najera[1], Wen-Rong Jiang[1], Sophie Le Pogam[1], Vincent Leveque[1], Han Ma[1], Yaping Tu[1], Rebecca Chan[1], Chiao-Wen Chen[1], Xiaoyang Wu[1], Raj Birudaraj[1], Steven Swallow[1], Joseph A. Martin[1], Nick Cammack[1], Heather Berns[1], Scott Fettner[2], David Ipe[1], Marie Mannino[2], Edward O'Mara[2], Carla Washington[1], Stuart Roberts[3], Graham Cooksley[4], Greg Dore[5], David Shaw[6], David R. Blue Jr.[1], Friederike Zahm[7], George Hill[1]

[1] Roche Palo Alto LLC, CA, USA; [2] F. Hoffmann-La Roche Ltd, Nutley, NJ, USA; [3] Alfred Hospital, Melbourne, Vic., Australia; [4] Royal Brisbane Hospital, Brisbane, Qld., Australia; [5] Christchurch Clinical Study Trust, Christchurch, New Zealand; [6] Royal Adelaide Hospital, Adelaide, SA, Australia; [7] F. Hoffmann La Roche, Basel, Switzerland

R1479 was identified as a selective inhibitor of HCV replication with high antiviral potency across HCV genotypes 1a and 1b isolates and a high barrier to resistance selection. Initial preclinical and clinical characterization of R1479 demonstrated suboptimal oral bioavailability because of limited absorption. A range of different types of R1479 prodrugs were synthesized and evaluated by characterization of physicochemical properties, Caco2 cell permeabilities and pharmacokinetics in rats and monkeys. Alkyl ester prodrugs were identified to substantially improve oral bioavailability of R1479, consistent with increased prodrug lipophilicity. R1626, the tri-isobutyrate ester prodrug of R1479 achieved a more than a five-fold increase in oral bioavailability and dose proportionality up to high dose levels. In concordance with dose dependent increases in plasma exposures of R1479, dose and time dependent mean viral load decreases of up to 3.7 $\log_{10}$ were observed in a 14 day multiple ascending dose monotherapy study in treatment naive patients with chronic HCV genotype-1 infection.

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