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**ABSTRACT 030**

## Antiviral Activity of Pradefovir Mesylate in Patients with Lamivudine-resistant HBV Infection: 24-week Interim Analysis from a Phase 2 Study

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BACKGROUND: Pradefovir mesylate (PDV) is a cytochrome P450 (CYP) 3A4-activated, liver-targeted prodrug of PMEA. The 24-week interim analysis of a randomized study comparing adefovir dipivoxil (ADV) 10 mg/d and PDV 5, 10, 20, and 30 mg/d demonstrated that PDV is safe, well tolerated, and has significantly greater anti-HBV activity than ADV with less systemic PMEA exposure.

OBJECTIVES: To evaluate the antiviral activity of PDV in patients with lamivudine (LAM) resistant mutations.

METHODS: HBV DNA was measured by COBAS Taqman® (lower limit of quantitation 169 copies/mL). Baseline samples from all 244 enrolled patients were assayed for YMDD mutations by the Bayer TruGene® HBV Genotyping kit.

RESULTS: 28 patients had evidence of LAM resistant HBV at baseline, 4 genotype B and 24 genotype C. Among PDV treated patients, 2 in the 30 mg group had L180M mutations without detectable YMDD mutations. Three had M204I mutation alone: 2 in the 5 mg and 1 in the 20 mg groups. The remaining 20 patients had an M204I or M204V mutation combined with the L180M mutation. Of these, 4, 3, 7 and 6 patients were in the 5 mg, 10 mg, 20 mg and 30 mg groups, respectively. Two of these, 1 in the 5 mg and 1 in the 10 mg groups also had detectable V173M mutation. In the ADV group, 1 patient had the L180M mutation and 2 had the M204I mutation. Results for antiviral activity are presented in the table, below.

| Treatment Groups | PDV 5 mg | PDV 10 mg | PDV 20 mg | PDV 30 mg | ADV 10mg |
|---|---|---|---|---|---|
| # of Patients with LAM resistant HBV<br>- Percent patients with HBV DNA < 400 copies/mL. | n = 6<br>17 | n = 3<br>33 | n = 8<br>38 | n = 8<br>50 | n = 3<br>33 |
| # of Patients without LAM resistant HBV<br>Percent patients with HBV DNA < 400 copies/mL. | n = 41<br>17 | n = 46<br>24 | n = 40<br>28 | n = 40<br>35 | n = 47<br>15 |

CONCLUSION: Although the number of patients with LMV resistance studied was small, the 24-week interim analysis suggests that both PDV 30 and ADV appear to be equally active against LAM resistant HBV and wildtype HBV.

**ABSTRACT 031**

## Three-dimensional Pharmacophore Modeling of Hindered Nucleoside Analogs (HNAs) as Inhibitors of the Hepatitis C Virus NS5B Polymerase

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BACKGROUND: The hepatitis C virus has infected an estimated 1-3% of the world population, exceeding 170 million individuals. Current therapies based on

combinations of pegylated interferons and the broad spectrum antiviral ribavirin are ineffective in a significant proportion of cases, and are associated with the occurrence of severe side effects. A growing patient population is in urgent need for novel therapies that could address a clearly unmet medical need. The HCV NS5B RNA-dependent RNA-polymerase (RdRp) is a central enzyme in the replication of the virus, and has become a target of choice for the screening and design of new inhibitors which, in principle, should interfere with viral replication. Under this perspective, we recently synthesized and evaluated a series of hindered nucleoside analogs (HNA), possessing notable anti-*Flaviviridae* activity, as inhibitors of HCV RdRp. Starting from these molecular sets, we developed a 3D chemical feature-based pharmacophore model to be used in the accelerated discovery of novel, more potent hepatitis C virus inhibitors.

METHODS: In this work we designed a molecular modeling strategy using some molecular test sets selected from HNAs as potential HCV polymerase inhibitors. Accordingly, 3D chemical feature-based pharmacophore models were developed for each series of compounds. These simple but highly effective models were then used to predict the anti-*Flaviviridae* activity of all derivatives previously synthesized in our laboratories, achieving an outstanding agreement between experimental and simulated data. For the most promising compounds, the interactions with the HCV RdRp was further studied, both qualitatively and quantitatively, by detailed molecular modeling techniques carried out in the framework of the Molecular Mechanics/Poisson-Boltzmann Surface Areas (MM/PBSA) computational method.

RESULTS: The developed 3D pharmacophore models allowed to correctly predict the activities for all compounds belonging to the different HNA sets considered. These results demonstrate that the simple models derived in this study can be considered as a useful tool in designing new leads based on HNA scaffolds as anti-*Flaviviridae* agents. Furthermore, atomistic molecular dynamics simulations allowed clarifying in details the interactions between the most active compounds and their most probable viral target, the HCV RdRp.

CONCLUSIONS: A series of 3D chemical feature-based pharmacophore models were elaborated for different series of hindered nucleoside analogs showing anti-*Flaviviridae* activity using a quantitative approach. The models were highly predictive for all compound sets considered. More importantly, the results of these studies, coupled with detailed molecular simulation studies, provided confidence for the utility of the selected chemical feature-based pharmacophore models in the development of new compounds with desired anti-*Flaviviridae* biological activity by computer virtual screening and characterization.

**ABSTRACT 032**

## Dual Inhibition of HCV and HIV: A Ring-expanded ("Fat") Nucleoside Exhibits Highly Potent *In Vitro* Inhibitory Activity Against Both Viruses

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HCV is a major co-infection in patients infected with HIV, and a number of them ultimately die of end-stage HCV-related complications including liver cirrhosis and hepatocellular carcinoma. Therefore, a drug with dual inhibitory characteristics against both viruses is highly desirable. We report here the synthesis and antiviral activities of a ring-expanded ("fat") nucleoside analogue that inhibits both HCV and HIV *in vitro* with $EC_{50}$ values ranging in nanomolar and micromolar concentrations, respectively, with high therapeutic indices against both viruses suggesting little or no toxicity to the host cell lines. The anti-HCV activity was evaluated using two different *in vitro* quantitative assays employing the subgenomic HCV replicon system in stably transfected human hepatoma BM 4,5 cells as well as the HCV RNA replicon system with a stable luciferase (LUC) reporter. The *in vitro* anti-HIV activity was determined by assaying the RT (reverse transcriptase) activity in HIV-infected MT-4 cell line treated with and without the inhibitor.