Objective

1. Retrospectively evaluate abnormality and pharmacokinetic changes in select hepatic genes and measured parameters in a panel of Hepatitis B (HB) and human liver cell lines.

2. Characterize the in vitro metabolic profiles of ELND006 generated with the HepatoPac system.

Methods

1. ELND006 was evaluated in both human liver microsomes (HLM) and HepatoPac hepatocytes (HPH) using a metabolite profiling assay developed in CLaM (Cytometry and Mass Spectrometry Analysis). Metabolites were identified based on accurate mass, retention time, and pattern-matching against a library of known metabolites. This approach allowed for the discovery of uncharacterized metabolites that are not amenable to traditional metabolite identification methods.

2. Additional studies were conducted using an integrated panel of hepatocytes (HepiScape, HepiScape Corporation, MedWithout), bringing in 17 rat hepatocytes not shown. Parallel quantitation of basic metabolic parameters was achieved using microsomal binding or drug lipophilicity data. The proposed metabolic pathway in human and monkey based on the formation of characterized metabolites from specific mass transitions.

3. Qualitative assessment using MS/MS transitions of liver metabolites produced in plated human hepatocytes (HepiScape). HepiScape demonstrated good agreement with prior in vivo data and data generated in vitro (Figure 4b).

Discussion

- Prevention of clearance from very late time courses using in vitro systems can be challenging if it is the only approach to obtaining a result.
- While in vitro drug inhibition studies that measure the actual-unfolded circulating concentration of CL, the actual-unfolded concentration in multiple nonclinical species.
- Optimization of CL was still overpredicted (on the same magnitude as allometry).
- Qualitative assessment using MS/MS transitions of liver metabolites produced in plated human hepatocytes (HepiScape). HepiScape demonstrated good agreement with prior in vivo data and data generated in vitro (Figure 4b).

References


Assessment was empirically scaled using simple allometry (CL/F) and allometry using maximum life span (S) and brain weight (B) (Table 2). The values ranged from 0.001 to 0.0101 L/h/kg (allometry, CL/F) shown in Figure 5. Allometry using S and B was scaled with preclinical PK data obtained from mouse, rat, dog and monkey. Animals were approximately one in rats and monkeys (data not shown). Physiological parameters were based on the fact that the blood to plasma partitioning of...