**Introduction**

- Apoptosis, or programmed cell death, is characterized by distinctive morphological changes such as cell shrinkage, plasma membrane blebbing and nuclear condensation.
- Biochemically, a hallmark of apoptosis is the activation of caspases, which are a family of cysteine proteases responsible for the execution of the apoptotic program.
- Caspase-8 and -9 can be activated in different ways and under the regulation of signals that lead to their functional execution.
- Apoptosis can be studied in different ways and under the regulation of signals that lead to their functional execution.

**Methods**

- Two randomized, double-blind, placebo-controlled Phase I studies were performed exploring the safety of healthy male subjects and 6 healthy female subjects following administration of single and multiple oral doses of GS-9450 (5 mg, 40 mg, and 120 mg). Safety data were analyzed by intention-to-treat.  
- The most frequent adverse events observed during the study were abdominal pain and myalgia and occurred with similar frequency in placebo and GS-9450 treated subjects.

**Results**

**Safety**

- Overall, GS-9450 was well tolerated with no serious (SAE) or severe adverse events reported.
- The most frequently reported AE was headache.
- No unexpected safety issues were observed and no AEs were mild.
- There was no evidence for a dose-related increase in the incidence or severity of AEs.
- One male subject discontinued dosing during the MAD study due to development of a rash of mild severity.  No effects were observed on vital signs measurements, ECG recordings, continuous cardiac monitoring or safety laboratory tests.

**Pharmacokinetics**

- The pharmacokinetic parameters of GS-9450 following single and multiple, escalating oral doses were assessed in 18 healthy male and female subjects.  
- For additional information on GS-9450 please also see poster #969.

**Conclusions**

- Single oral doses of 5 to 120 mg and multiple oral doses of 40 to 120 mg of GS-9450 were well tolerated by healthy male and female subjects.
- The half-life of GS-9450 supports once-daily dosing and no evidence was found for a significant change in the PK of GS-9450.
- Phase II trials with GS-9450 are currently being performed in chronic HCV infected and NASH patient populations.

**Acknowledgements**