Hepatotoxicity: Severe drug-induced liver injury with fatal outcome occurred in 0.3% of patients treated with STIVARGA®.

Common AEs During Treatment with STIVARGA
- Hyperbilirubinemia was observed in 33% vs. 12% of STIVARGA- and placebo-treated patients, respectively.
- The incidence of Grade 3 rash (7% vs 0%) was higher in STIVARGA-treated patients than in the placebo group. STIVARGA caused an increased incidence of hand-foot skin reaction (HFSR) (also known as palmar-plantar erythrodysesthesia [PPE]) and severe rash.

Dose Modifications Procedures for Other AEs
In addition to liver and rash, additional dose modifications and measures for other AEs have been developed.

Common AEs During Treatment with STIVARGA
- STIVARGA caused an increased incidence of HFSR and severe rash requiring dose modification.
- The overall incidence of HFSR in STIVARGA was 9% vs. 1% in placebo-controlled trials. A high proportion of patients with HFSR continued to receive STIVARGA, and the severity was high in the first 3 cycles, every 6 weeks for cycles 4-6 and every 8 weeks after cycle 6.
- The incidence of Grade 3 rash (7% vs 0%) was higher in STIVARGA-treated patients than in the placebo group. STIVARGA caused an increased incidence of HFSR and severe rash requiring dose modification.

**Hypothyroidism incidence based on subset of patients with normal TSH and no thyroid supplementation at baseline.

**Recommended dose modifications and measures for HFSR have been developed.

**Figure 2. Grading HFSR

**Cardiovascular:
- Severe drug-induced liver injury with fatal outcome occurred in 0.3% of patients treated with STIVARGA®.
- STIVARGA caused an increased incidence of myocardial ischemia compared to best supportive care (BSC) in the GRID study, the median duration of therapy was 22.9 (range 0.1, 50.9) weeks for patients treated with STIVARGA.
- STIVARGA caused an increased incidence of myocardial ischemia compared to best supportive care (BSC) in the GRID study, and the median duration of therapy was 22.9 (range 0.1, 50.9) weeks for patients treated with STIVARGA.

**References