Child-Pugh versus NCI-ODWG categorization for hepatic impairment studies - observations from a renal and hepatic impairment study with darolutamide, a novel investigational androgen receptor antagonist

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Background: According to FDA and EMA guidance for hepatic impairment studies, Child-Pugh classification should be used. In oncology, criteria from the National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) are also used to classify hepatic dysfunction. Within a renal and hepatic impairment study on darolutamide, both criteria were used to classify hepatic impairment.

Methods: As part of a Phase I, non-randomized, open-label study (NCT02894385), subjects with hepatic or renal impairment were compared with a control cohort of age- and weight-matched healthy subjects (cohort 1). In cohort 2, subjects were included based on moderate hepatic impairment (Child-Pugh B) and additionally assessed using NCI-ODWG criteria. Cohort 3 included subjects with severe renal impairment based on estimated glomerular filtration rate (15-29 ml/min/1.73 m²). Subjects received a 600 mg oral dose of darolutamide. Primary PK variables were darolutamide C_{max} and AUC₍₀₋₄₈₎; safety assessment was primarily based on documented adverse events.

Results: Nine subjects were included in cohort 2 according to Child-Pugh B; the mean AUC₍₀₋₄₈₎ and C_{max} of darolutamide were 1.9- and 1.5-fold higher respectively, versus healthy controls (n=10). The additionally applied NCI-ODWG criteria classified liver function in seven cohort 2 subjects as normal, one as mild, and one as moderate dysfunction; AUC₍₀₋₄₈₎ of darolutamide in these two subjects with hepatic dysfunction was approximately 3-fold higher versus controls. Four of the seven subjects with normal NCI-ODWG-rated liver function showed additional renal impairment. Severe renal impairment (cohort 3) resulted in increased mean darolutamide exposure versus healthy controls. Three subjects (10.3%; two in cohort 1, one in cohort 3), experienced one mild treatment-emergent adverse event (not considered related to darolutamide).

Conclusions: Moderate hepatic impairment and severe renal impairment increased darolutamide exposure. Using the Child-Pugh system for classification of moderate hepatic impairment, mean darolutamide exposure was lower compared with the exposure in the two subjects categorized as mildly or moderately hepatically impaired according to the NCI-ODWG criteria. The additional impact of renal impairment in hepatically impaired subjects should be considered during data evaluation. Due to the good safety profile of darolutamide, no overall increase in safety risk is expected in subjects with organ impairment.