17-BI-1206-02 Phase 1/2a Clinical Trial of BI-1206, a Monoclonal Antibody to FcγRIIB, in Combination with Rituximab in Subjects with Indolent B-Cell Non-Hodgkin Lymphoma That has Relapsed or is Refractory to Rituximab

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Introduction

BI-1206 is a fully-human IgG1 monoclonal antibody that exquisitely recognizes and blocks FcγRIIB (also referred to as CD32b). BI-1206 enhances the activity of anti-CD20 antibodies such as rituximab by preventing interaction with FcγRIIB and may thus overcome resistance to those treatments. BI-1206 is currently in clinical investigation in combination with rituximab for the treatment of indolent NHL.

Methods

The safety and tolerability profile of BI-1206 in combination with rituximab is currently investigated in the Phase 1/2a clinical trial 17-BI-1206-02. The study population includes patients with follicular lymphoma (FL), marginal zone lymphoma (MZL), and mantle cell lymphoma (MCL) who have relapsed or are refractory to rituximab. BI-1206 and rituximab are administered as i.v. infusions once per week for 4 weeks. In Phase 1a, a 3+3 study design is used, with escalating doses of BI-1206 and a fixed dose of rituximab (375 mg/m^2), with the aim of selecting the RP2D of BI-1206 for the expansion cohort in Phase 2a.

Patients showing clinical benefit, are eligible for continued maintenance therapy with dosing of BI-1206 and rituximab every 8 weeks.

The assessment of the pharmacokinetics (PK) of BI-1206 included non-compartmental analysis (NCA), and the assessment of the pharmacodynamics (PD) included receptor occupancy (RO%). PK modelling was conducted to further characterize the PK behavior and to provide predictions of upcoming dose levels. In addition, the effect of BI-1206 on the PK of rituximab was investigated by comparing PK parameters of rituximab to literature values of rituximab monotherapy.

Results

Up to 100 mg BI-1206 has so far been administered in combination with rituximab (375 mg/m^2). Increasing doses of BI-1206 from 30 mg to 70 or 100 mg gave rise to a supra-proportional increase in C_{max} as well as an increase in the half-life of BI-1206. A trend of accumulation after consecutive doses was also seen. When comparing the serum-concentrations against the associated RO% of CD32b there is a trend that higher dose levels are close to fully saturating the receptors immediately after dosing and up to 72 hours. It is therefore likely that increasing the dose further, will give rise to full receptor saturation, which should be maintained for an extended period.

Clinical response, assessed by reduction of tumour size, has been observed at the 70 mg cohort. This at a dose which typically does not saturate receptors for the entire dose interval. It may therefor be speculated that doses which enable full RO% over the entire dosing interval, may show additional clinical benefit for patients.

PK modelling showed that there was a significant contribution of a non-linear component on the elimination of BI-1206, which may be attributed to receptor binding. A two-compartment model with linear (non-saturating) and non-linear (saturating) elimination best describes the data. Using the generated model for predictions of upcoming doses revealed that doses relatively close to the ones already administered may be sufficient for full receptor saturation during the entire dosing interval.

Finally, the C_{max} after one dose of rituximab was in the same range as previously reported values, indicating no substantial effect on the PK of rituximab. Consequently, at the current dose levels, there is no obvious need for dose-adjustments for rituximab.

Conclusions

This report presents preliminary data of the clinical trial 17-BI-1206-02, where BI-1206 is combined with rituximab. The presented data is encouraging, both in terms of first clinical response against tumors, as well as showing signs of overcoming target-mediated drug disposition, which may allow weekly or even less frequent dosing at clinically relevant dose levels.