**ADCT-602 (hLL2-cys-PBD), a new site-specifically conjugated, pyrrolobenzodiazepine (PBD) dimer-based antibody drug conjugate (ADC) targeting CD22-expressing B-cell malignancies**

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**Introduction**

1. CD22 is a transmembrane glycoprotein whose expression is restricted to the B-cell lineage. CD22 is also highly expressed on most myeloma/plasma cells, including follicular lymphomas (FL), marginal zone lymphomas (MZL), mantle cell lymphoma (MCL), diffuse large B-cell lymphoma (DLBCL), small lymphocytic lymphoma (SLL) and chronic lymphocytic leukemia (CLL). Moreover, CD22 is expressed in >90% of cases of B-precursor acute lymphoblastic leukemia (ALL). [Figure 1: CD22 structure]

2. The differential and favourable expression profile of CD22 in tumour versus normal tissue, together with its rapid internalization upon binding ligand or antibody, make CD22 a unique target for antibody-drug conjugates (ADC) mediated treatment of B-cell malignancies.

3. ADCT-602 is an ADC composed of an engineered version of the humanized anti-CD22 mAb gpl904, site-specifically conjugated to the PBD drug linker toxin (Fig. 2A) to achieve antibody ratio 1:7PBD following internalization. CD22 expression is highly cytostatic and cross-links in the DNA minor grooves.

**Aim of this study**

Characterization of the in vitro mechanism of action and in vivo efficacy, tolerability and pharmacokinetics (PK) of ADCT-602.

**Material & Methods**

Cytotoxicity of ADCT-602 was determined by the CellTiter Glo (Promega) luminescent cell viability assay. Baseline cell counts were determined and viability was calculated as the ratio of treated cell viability at each time point to the baseline cell count. The half-life was determined by non-linear regression analysis of time versus drug concentration.

**Results**

**CD22 expression:** The single cell population assessment was carried out on Ramos cells and HL-60 cell line treated with ADCT-602 at three different doses. The mean reduction in the mean fluorescence of CD22 in Ramos was 30.1% ± 3.2% and 12.3% ± 3.2% in HL-60 cells. [Figure 2: CD22 expression]

**Toxicology:** ADCT-602 was administered intravenously to C57BL/6 mice at 0.5 mg/kg and 3 mg/kg on day 1 and day 5. Tumour burden at day 10 was determined. ADCT-602 induced a significant reduction in tumour burden compared to control. [Figure 3: Toxicology]

**PK analysis:** ADCT-602 was administered intravenously to male Sprague-Dawley rats at 3 mg/kg. Blood was sampled at pre-dose and 5, 15, 30, 60 minutes and 2, 4, 6, 8, 12 and 24 hours post-dose. Radioactivity in plasma was determined by liquid scintillation counting. [Figure 4: PK analysis]

**In vivo antitumour efficacy:** ADCT-602 was administered intravenously to athymic Balb/c mice bearing Raji xenografts on day 0. Tumour burden at day 10 was determined. ADCT-602 induced a significant reduction in tumour burden compared to control. [Figure 5: In vivo antitumour efficacy]

**In vivo pharmacodynamics:** ADCT-602 was administered intravenously to athymic Balb/c mice bearing Raji xenografts on day 0. Tumour burden at day 10 was determined. ADCT-602 induced a significant reduction in tumour burden compared to control. [Figure 6: In vivo pharmacodynamics]

**Conclusions**

1. ADCT-602 showed potent in-vitro cytostatic effects in CD22-positive Raji (CD22) cell line compared to control. [Figure 7: In-vitro cytostatic effects]

2. ADCT-602 was efficiently internalized into Ramos cells and trafficked to the lysosomes. It induced DNA adducts, which persisted for at least 48 hours in vitro, and it mediated bystander cell death of CD22-negative Ramos cells after treatment with ADCT-602. [Figure 8: In vivo antitumour efficacy in Ramos xenograft model]

3. ADCT-602 administered at 1 mg/kg showed significant antitumour activity in multiple xenograft tumour models, including human primary lymphoma. [Figure 9: In vivo pharmacodynamics]

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**References**