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An investigation of the *in vitro* and *in vivo* pharmacology of a selective inhibitor of Aurora B kinase (AZD1152) in AML

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AZD1152 is a specific aurora kinase inhibitor with selectivity for Aurora B kinase, designed to target cell division in proliferating tumour cells. AZD1152 is a highly soluble pro-drug developed for parenteral administration that is cleaved completely in human plasma to yield the active drug substance AZD1152-HQPA. Inhibition of Aurora B kinase *in vitro* with AZD1152-HQPA reduces histone H3 phosphorylation substrate for Aurora kinase activity and inhibits cytokinesis, thus inducing cellular multi-nucleation and polyploidy, leading to cell death and apoptosis.

AZD1152-HQPA shows anti-cancer activity *in vitro* against a range of leukaemic cell lines and primary leukaemic blasts. Drug-induced changes in cell cycle distribution, including apoptosis (sub-G1) and G2/M (4N DNA) were revealed by flow cytometry. A polyploid population (>4N DNA) was also observed, confirmed by karyotype analysis. Fluorescence microscopy and flow cytometry indicated that exposure of these cells to AZD1152-HQPA suppressed phosphorylation of serine-10 on histone H3. In immunocompromised rodents (nude or NOD/SCID mice) bearing a human AML tumour xenograft (subcutaneous or orthotopic HL-60), AZD1152 shows significant anti-tumour efficacy. In the subcutaneous model, complete regressions were observed in 9/11 animals, whilst in the orthotopic model engraftment of HL-60 cells to the bone marrow was reduced significantly.

AZD1152 shows clear effects in preclinical *in vitro/in vivo* models of AML. These data provide a scientific rationale to investigate AZD1152 in a clinical AML setting. AZD1152 is currently being evaluated in Phase I clinical trials.