

## **Description of Additional Supplementary Files**

### **File Name: Supplementary Data 1**

**Description:** HDX-MS data for the HUWE1<sup>HECT</sup>~Ub proxy and HUWE1<sup>HECT</sup> in the presence of BI8626, BI8622, and DMSO (as a control), respectively.

### **File Name: Supplementary Data 2**

**Description:** global quantitative and diGly proteomic data from HEK293 cells upon BI8626 treatment (15  $\mu$ M; 24h) compared to a DMSO control.