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**Paper Poster Session VI**

**Tedizolid**

## Human sulfotransferase (SULT) reaction phenotyping of tedizolid

M. Niehues[1], M. Varoglu[1], L. Nguyen[1], H. Blanchette[1], S. Flanagan[2]

[1]*Bayer Health Care, Wuppertal, Germany*

[2]*Cubist Pharmaceuticals, San Diego, USA*

**Objectives:** Tedizolid is a novel oxazolidinone antibacterial with potent activity against a wide range of Gram-positive pathogens. It was recently approved by the US Food and Drug Administration for the treatment of acute bacterial skin and skin structure infections (ABSSSI) and it is now under review by the European Medicines Agency for the treatment of complicated skin and soft tissue infections (cSSTI). Tedizolid elimination in humans is primarily via hepatic excretion as a non-circulating sulfate-conjugate. Polymorphisms in SULTs have not been reported to significantly change the elimination of drugs to date, but metabolism of a drug by a single SULT isoform could lead to increased potential for drug interaction. Results of the *in vitro* studies to identify the SULT isoforms involved in the metabolism of tedizolid are described herein.

**Methods:** Incubation mixtures contained 50 mM phosphate buffer (pH 7.4), 5 mM $MgCl_2$, 1 µM or 10 µM tedizolid and the respective protein in a total volume of 250 µL. SULT isoforms were all used at a final concentration of 0.1 mg protein/mL with human liver and intestine cytosol at 0.5 mg protein/mL. Tedizolid was dissolved in acetonitrile/distilled water (1: 1) resulting in a concentration of 1% organic solvent in the final incubation mixture. The reaction was initiated by addition of 3'-phosphoadenosine-5'-phosphosulfate (PAPS, 55 µM) cofactor after a 3-minute pre-warming at 37°C. Incubations were terminated after 30 minutes by addition of 125 µL acetonitrile. The formation of tedizolid-sulfate from tedizolid incubated in pooled human liver cytosol (HLC) and human intestinal cytosol (HIC) or by individual SULT isoforms (SULT1A1, 1A2, 1A3, 1B1, 1C1, 1C2, 1C3, 1E1, 2A1, 2B1a, 2B1b, 4A1, and 6B1) fortified with PAPS was measured by LC-MS.

**Results:** Tedizolid sulfonation occurred in both HLC and HIC, with turnover rates of tedizolid in HLC that were at least 2-fold higher than in HIC. Studies with individual isoforms indicated that the biotransformation of tedizolid was catalyzed by SULT1A1, SULT1A2 and SULT2A1 enzymes which are expressed in human liver and intestinal tissue. Due to their tissue specific expression levels, SULT1A1 and SULT2A1 in liver are considered as the more relevant isoforms and site of metabolism, in comparison to SULT1A2 which is reported to be expressed at only very low levels in all human tissues.

**Conclusion:** Tedizolid sulfate formation *in vitro* occurs in human liver and intestinal cytosol. As multiple human SULT isoforms are capable of metabolizing tedizolid, no clinically relevant effects on tedizolid plasma exposure are expected to arise due to polymorphic SULT enzymes or drug interactions.