# A novel macrolide/fluoroketolide, CEM-101, reverses corticosteroid insensitivity under oxidative stress via PI3K pathway inhibition

## Abstract 3527

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### Rationale:

We have recently demonstrated that the reduction of histone deacetylase (HDAC)2 activity via PI3K activation causes corticosteroid (CS) insensitivity in COPD (ATS 2007). Here we show that CEM-101, a novel macrolide/fluoroketolide, which has potent activities against many bacteria causing pneumonia (starting Phase 2), reverses oxidative stress-dependent CS insensitivity via inhibition of PI3K signaling.

### Methods:

CS sensitivity was determined by calculation of $IC_{50}$ value of dexamethasone on TNF$\alpha$-induced IL-8 production in U937 monocytic cell line. HDAC activity and phosphorylation level of Akt as a marker of PI3K activation were measured by fluorescence based activity assay and western blotting, respectively. HDAC2 mRNA expression were also determined in A549 type II alveolar epithelial cell line. Cells were exposed to oxidative stress such as hydrogen peroxide ($H_2O_2$) or cigarette smoke extract (CSE) to induce steroid insensitivity.

### Results:

Oxidative stress decreased CS sensitivity with concomitant down-regulation of total HDAC activity/HDAC2 expression and increased Akt phosphorylation. Treatment with CEM-101 (10 $\mu$M) restored CS sensitivity in $H_2O_2$ exposed cells. In addition, CEM-101 (10 - 100 $\mu$M) restored HDAC activity and HDAC2 expression reduced under oxidative stress and also inhibited Akt phosphorylation, which effects were more potent than those of any macrolides currently used clinically.

### Conclusions:

CEM-101 restores CS sensitivity in oxidative stress-dependent CS insensitive model via enhancement of HDAC activity/expression due to PI3K signaling inhibition. This novel fluoroketolide, CEM-101, has potential for a novel treatment of COPD or severe asthma, which are steroid insensitive.