Results Among 323 participants, 89% were female, 39% Asian, 11% African American, 22% Hispanic of any race, and 29% White. Mean age was 45±14; mean age at diagnosis 29 ±12. Nearly half of respondents had a college degree. SDI at the baseline study visit ranged from 0 to 10 points, mean 1.8 ±2.0; 70% of the cohort had SDI>0. The regression model showed strong evidence (p=0.01) for interaction of age of diagnosis with race/ethnicity. As seen in the figure 1, SDI scores in racial/ethnic minorities were much higher among those diagnosed at younger ages; this relationship was not seen among whites.

Conclusions In this multi-ethnic cohort of SLE patients, the association of diagnosis age and disease damage varied according to race/ethnicity, with whites diagnosed at younger ages accumulating less damage than those in other racial/ethnic groups diagnosed at comparable ages. Future research should examine if these differences are due to phenotypic differences among the groups, diagnostic delays, or other access to care issues.

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214 RELATIONSHIP BETWEEN SERUM LEVEL OF RENALASE AND LUPUS NEPHRITIS ACTIVITY

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Background (LN)Lupus nephritis is a major risk for overall morbidity and mortality in SLE (Systemic lupus erythromatosis), and despite potent anti-inflammatory and immunosuppressive therapies still ends in Chronic Kidney Disease(CKD) or End Stage Renal Disease (ESRD) for too many patients. Renalase is a novel, kidney secreted cytokine-like protein that promotes cell survival.

Aim of the work studying the relationship between level of Human Serum Renalase (RNLS) with LN and its role in the disease activity and progression.

Methods For The current cross-sectional study 23 healthy controls and 48 patients with LN were screened and 30 subjects were selected These patients were subdivided into two equal groups according to disease activity measured by SLEDAI (SLE Disease Activity Index). Human Serum Renalase (RNLS) concentration was measured by a highly sensitive, commercial sandwich enzyme immunoassay which uses (RNLS) antibody to capture Renalase from serum. Assessment before and after treatment was done for 17 patients who received prednisone and immunosuppressive therapy were recruited and followed up for three months to evaluate the serum renalase levels before and after treatment.

Results The level of renalase was significantly higher in LN patients compared to healthy controls, (P value<0.001). Moreover, patients with active LN had higher serum renalase levels compared to patients with inactive LN(P value<0.005) Serum renalase levels were positively correlated with SLEDAI, 24 hour urine protein excretion, ds-DNA and ESR and CRP but inversely correlated with serum C3 and the class (especially in prolferative type (Class III, IV, more than class V). Renalase amounts decreased significantly after three-months of standard therapy. Also we found there is insignificant difference of renlase level according to treatment by MMF(mycophenolate mofetil) and Cyclophosphamide during and after activity (P value=0.655, 0.550)

Conclusions Serum renalase levels were correlated with disease activity in LN. Serum renalase might serve as a potential indicator for disease activity in LN.

215 FIRST-IN-MAN STUDY EVALUATING THE SAFETY, TOLERABILITY, PHARMACOKINETICS AND CONCENTRATIONQT ANALYSIS OF THE NOVEL BTK INHIBITOR EVOBRUTINIB (M2951) IN HEALTHY VOLUNTEERS

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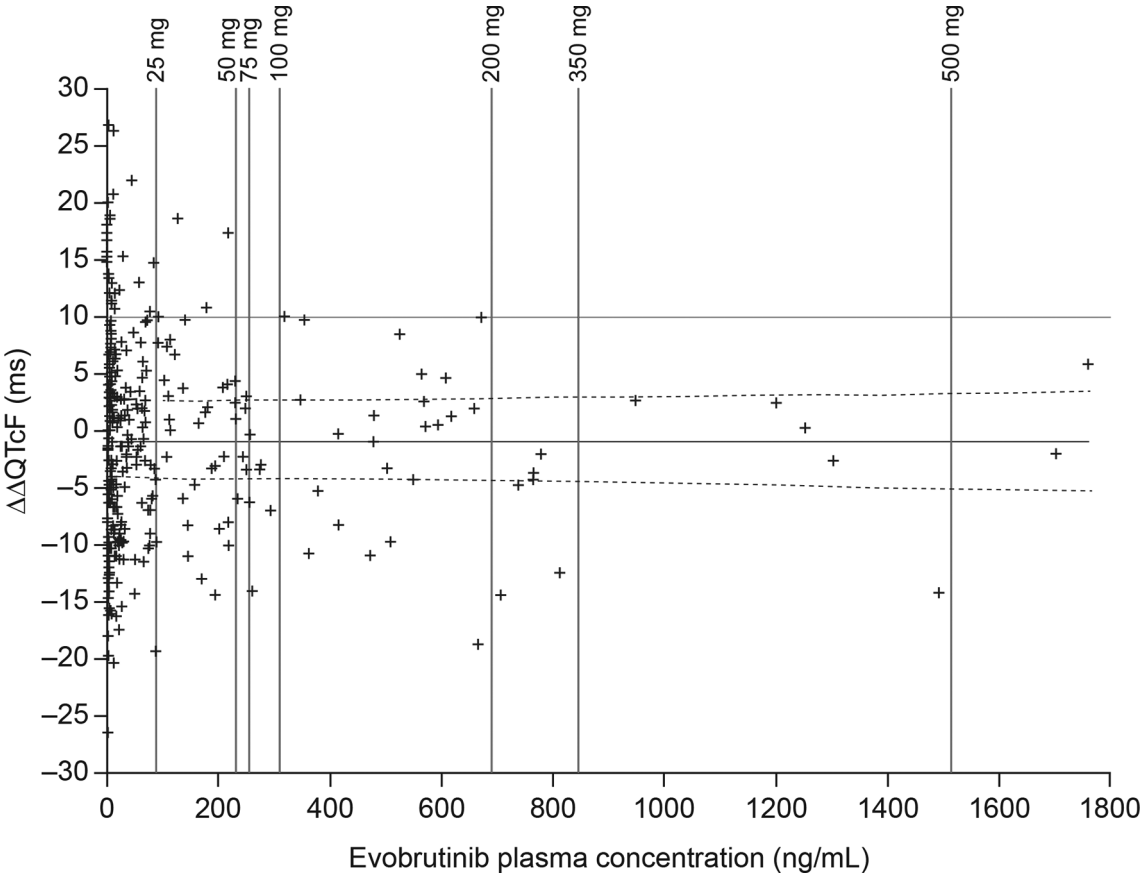
Background Brutons tyrosine kinase (BTK) regulates B-cell receptor signaling and is a rational target for B-cell driven pathologies, including SLE. Evobrutinib (M2951) is a highly specific, oral inhibitor of BTK that demonstrated efficacy in preclinical models of autoimmune disease. This first-in-man study investigated the safety, tolerability, and pharmacokinetics (PK) of evobrutinib in healthy volunteers and examined the relationship between evobrutinib exposure and changes in QT interval.

Methods This was a single-center, Phase I, double-blind, placebo-controlled trial. In Part 1, 48 healthy participants in six successive dose cohorts (25, 50, 100, 200, 350, 500 mg) were randomized (6:2) to a single oral dose of evobrutinib or placebo. In Part 2, 36 participants in three ascending dose cohorts (25, 75, 200 mg/day) were randomized (9:3) to evobrutinib or placebo once daily for 14 days. Safety and tolerability were assessed following single and multiple dosing, and PK parameters determined by non-compartmental methods. Change from baseline in QT interval was obtained from 12-lead electrocardiogram recordings and corrected for heart rate by Fridericias method (QTcF).

Results Treatment-emergent adverse events (TEAEs) with evobrutinib were mostly mild, occurring in 25% of participants after single dosing, and 48% after multiple dosing. The nature and incidence of TEAEs were similar among evobrutinib and placebo groups, with no apparent dose relationship regarding the frequency or type of TEAEs. Evobrutinib showed rapid absorption (tmax ~0.5 hour), short half-life (~2 hour), and dose-proportional PK following single and multiple dosing, with no accumulation or time dependency on repeat dosing. ConcentrationQTcF analyses revealed no significant exposureeffect relationship. Based on a linear mixed-effects model for change from baseline in QTcF (QTcF), the slope of the relationship between mean placebo-adjusted QTcF (QTcF) and concentration was negative and close to zero (0.00027 ms/ng/mL; p=0.86; figure 1). The predicted QTcF effect at geometric mean Cmax for the highest dose (1512 ng/mL) was 1.16 ms, with an upper limit of 3.26 ms for the 90% two-



Abstract 215 Figure 1 Relationship between evobrutinib concentration and QTcF

sided bootstrapped confidence interval, which is well below the 10 ms threshold of regulatory concern (ICH-E14 guidance).

Conclusions Evobrutinib was well-tolerated in healthy volunteers, with predictable PK and no prolongation of QT interval (QTcF). Evobrutinib is undergoing clinical investigation in SLE and other autoimmune diseases.

Funding Source(s): Merck KGaA, Darmstadt, Germany

216 INHIBITION OF BRUTONS TYROSINE KINASE (BTK) PREVENTS INFLAMMATORY MACROPHAGE DIFFERENTIATION: A POTENTIAL ROLE IN SLE

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Background Brutons tyrosine kinase (BTK) mediates B cell receptor (BCR) and Fc receptor (FcR) signaling in several hematopoietic cell lineages, including B cells, macrophages and neutrophils. The BTK inhibitor evobrutinib silences B cells and prevents innate immune activation via FcR and has been shown to be efficacious in a preclinical model for SLE. Macrophages can have pro-inflammatory and anti-inflammatory properties and thus they play a crucial role in exacerbation versus control of autoimmune disease. BTK function has been implied downstream of certain cytokine receptors that control macrophage differentiation. The aim of this preclinical study was to investigate the effect of BTK inhibition on the differentiation and activation of monocytes and macrophages.

Methods Monocytes were isolated from the peripheral blood of healthy volunteers. BTK activation was analyzed by Western blot following a 30 min BTK inhibitor treatment and a subsequent granulocyte-macrophage colony-stimulating factor (GM-CSF) stimulation time course. Survival of GM-CSF differentiated M1 cells was analyzed by flow cytometry following AnnexinV/PI staining. Expression levels of interleukin (IL)−1ß and IL-10 were determined by quantitative polymerase chain reaction following 48 hours of GM-CSF stimulation and BTK inhibitor treatment. Tumor necrosis factor alpha (TNF-) levels in cell culture supernatants were measured by ELISA following overnight lipopolysaccharide stimulation and BTK inhibitor treatment. The uptake of apoptotic cells by M2 macrophages was analyzed by flow cytometry.

Results BTK was activated downstream of the GM-CSF receptor. In line with this finding, *in vitro* GM-CSF differentiated M1 macrophages underwent apoptosis upon BTK inhibition using evobrutinib. Monocytes treated with GM-CSF in the presence of BTK inhibitor secreted less TNF- and expressed