The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

GSK Medicine: dabrafenib (GSK2118436); trametinib (GSK1120212)
Study Number: 200997 also known as PGx7550
Title: PGx7550: PGx investigation of pyrexia by meta-analysis of dabrafenib/trametinib melanoma studies BRF113710, BRF113929, BRF113683 and MEK115306
Rationale: Dabrafenib (GSK2118436), a selective inhibitor of V600E/K mutated BRAF kinase, and trametinib (GSK1120212), a selective inhibitor of MEK1 and MEK2 kinases, are approved as single agents (US and EU) and in combination (US) for the treatment of advanced or metastatic melanoma with *BRAF* V600 mutation. Pyrexia, or fever, is one of the most common adverse events (AE) in subjects exposed to dabrafenib or a combination of dabrafenib and trametinib. The incidence of pyrexia is much higher in subjects treated with a combination of dabrafenib and trametinib (up to 70%) than with dabrafenib alone (25-30%). The majority of these AEs are transient and resolve after treatment interruption, while a small proportion (2-5%) of subjects develops serious non-infectious febrile events requiring extensive management. The underlying mechanism for development of pyrexia on treatment with dabrafenib alone or in combination with trametinib is not clear. Genetic variation may elucidate the mechanism of this AE and may help to predict patients at risk of developing pyrexia. Therefore, an exploratory pharmacogenetic (PGx) analysis was undertaken in subjects from four metastatic melanoma clinical studies (BRF113710, BRF113929, BRF113683 and MEK115306) to identify germline genetic variants that may be associated with the development of pyrexia.
Study Period: 21-March-2014 to 17-December-2014
Objectives: Identify germline genetic variants that may be associated with pyrexia in metastatic melanoma subjects treated with dabrafenib alone or in combination with trametinib in a meta-analysis of 4 melanoma studies.
Indication: Metastatic melanoma
Study Investigators/Centers: GSK conducted this exploratory pharmacogenetic analysis using DNA samples from subjects who provided informed consent for PGx during the conduct of clinical studies BRF113710, BRF113929, BRF113683 and MEK115306.
Research Methods: Genome wide genotype data generated for previous PGx evaluation (BRF116604/PGx6039) using the Illumina Human Omni Express plus Exome (OEE) BeadChip array were reused in this PGx investigation. Genome wide data for MEK115306 were generated using Affymetrix Axiom Biobank Plus GSK Custom array. Genome wide imputation was carried out to obtain missing genotype data for variants typed on the 2 genotyping platforms. Genetic variants were stratified into four tiers. Tier 1 included a functional variant (rs8099917) in *IL28B* gene that had shown marginal evidence of association (p = 0.006) with pyrexia in a prior analysis of dabrafenib monotherapy studies (BRF116604/PGx6039). Tier 2 included additional 46 variants in 25 candidate genes encoding proteins for cytokines and cytokine regulation, prostaglandin synthesis, signalling and activity, and dabrafenib transport and metabolism. Tier 3 included class I and II HLA alleles and tier 4 included the remaining variants on the genome wide platforms and imputed variants (n=6 million).
Data source: Clinical data was collected during the conduct of clinical studies BRF113710, BRF113929, BRF113683 and MEK115306.
Study Design: This exploratory pharmacogenetic study was a retrospective, non-interventional analysis to investigate association of genetic polymorphisms with pyrexia in subjects treated with dabrafenib alone or in combination with trametinib.
Study Population: The PGx analysis population consisted of subjects enrolled in clinical studies BRF113710, BRF113929, BRF113683 or MEK115306 who received dabrafenib alone or in combination with trametinib, who met the definition of a pyrexia case or control, provided written informed consent for PGx research and a blood sample for genotyping, were successfully genotyped, had valid phenotype data and passed genotyping quality control (QC). Of the 1031 subjects who consented for PGx research in the 4 clinical studies, 132 and 275 subjects met the definition of pyrexia case and control, respectively, and were selected for PGx analysis.
Study Exposures, Outcomes: All subjects being evaluated in this pharmacogenetic analysis received dabrafenib or dabrafenib and trametinib for the treatment of metastatic melanoma from the start of the clinical studies BRF113710, BRF113929, BRF113683 and MEK115306 or after crossover in case of subjects from the dacarbazine (DTIC) arm of BRF113683. Pyrexia was defined as any adverse event reported as pyrexia, hyperpyrexia, body temperature increased, or tumour associated fever and was divided into grades 1-4 according to *NCI Common Terminology Criteria*

for Adverse Events (CTCAE) v.4. A pyrexia case was defined as any metastatic melanoma subject with normal temperature at baseline (< 38 ºC) and developing an AE of pyrexia (CTCAE v.4.0 grade ≥2) while receiving dabrafenib alone or in combination with trametinib. A pyrexia control was defined as a metastatic melanoma subject with normal temperature at baseline and no fever despite sufficient exposure to dabrafenib or a combination of dabrafenib and trametinib (cumulative duration of exposure of at least 139-182 days across the clinical studies, corresponding to the time by which >90% of 'Cases' had an event of pyrexia).
Data Analysis Methods: Association with pyrexia case-control status was conducted using logistic regression. Prior to PGx analysis, non-genetic independent variables in the clinical studies were evaluated for association with pyrexia. The variables significantly correlated with pyrexia at p≤0.05 were included in the analysis model while testing for genetic effect. Melanoma subjects from the monotherapy and combination arm of MEK115306 were analyzed separately. Clinical studies analyzed previously in BRF116604/PGx6039 were re-analyzed for genome wide imputed variants. Summary statistics from these studies combined and the 2 arms of MEK115306 were then meta-analyzed using the inverse variance method. Genetic association analyses were conducted assuming an additive genetic model. HLA genotypes were imputed to 4-digit resolution from genome wide data.
Limitations: This exploratory pharmacogenetic analysis was conducted using clinical data and germline DNA obtained during the conduct of studies BRF113710, BRF113929, BRF113683 and MEK115306. The clinical trials were not designed to address specific genetic hypotheses. With 132 pyrexia cases and 275 controls, there was >80% power to detect associations of common genetic variants (minor allele frequency (MAF)>10%) with effects (odds ratios (ORs)) greater than 3 and 5 for the candidate gene and whole genome analyses, respectively. However, the power was limited to detect genetic associations with smaller effect sizes or of less common genetic variants. These analyses are exploratory and any associations identified would generally require confirmation in an independent set of data.
Study Results: The genetic variant (rs8099917) in *IL28B* (tier 1) was not associated with pyrexia in subjects treated with dabrafenib or combination of dabrafenib and trametinib. No other functional candidate genetic variants (tier 2), HLA variants (tier 3) or genome-wide variants (tier 4) were significantly associated with pyrexia, assuming Bonferroni adjustment for multiple tests per tier.
Conclusions: The lack of association of the *IL28B* candidate variant, rs8099917 with pyrexia despite high statistical power (>95%) suggests this SNP does not have an effect on dabrafenib induced pyrexia. The lack of statistically significant associations for any of the tiers of variants analyzed suggests that a large genetic effect on pyrexia is unlikely. Much larger sample sizes would be needed to detect any small to moderate genetic effects that may exist.

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