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: 202050 also known as PGx7607
Title: PGx7607: PGx investigation of pyrexia by meta-analysis of dabrafenib/trametinib melanoma studies BRF113710, BRF113929, BRF113683,MEK115306 and MEK116513
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 the 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. Germline 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 five metastatic melanoma clinical studies (BRF113710, BRF113929, BRF113683, MEK115306 and MEK16513) to identify germline genetic variants that may be associated with the development of pyrexia.
Study Period: 03-October-2014 to 22-January-2015
Objectives: Primary: Identify germline genetic variants that may be associated with pyrexia in a meta-analysis of metastatic melanoma subjects treated with dabrafenib alone or in combination with trametinib from 5 melanoma studies. Secondary: Identify germline genetic variants that may be associated with either 1) early onset pyrexia (pyrexia developing within first 8 weeks of treatment) or 2) time to pyrexia onset in a meta-analysis of metastatic melanoma subjects treated with dabrafenib alone or in combination with trametinib from 5 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, MEK115306 and MEK116513.
Research Methods: Genome wide genotype data generated for previous PGx evaluations using either the Illumina Human Omni Express plus Exome (OEE) BeadChip array (BRF116604/PGx6039) or Affymetrix Axiom Biobank Plus GSK Custom array (200997/PGx7550) were reused in this PGx investigation. Genome wide data for MEK116513 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 and to obtain genotype data for class I and II *HLA* gene variants (n=50). A total of 6 million genetic variants (directly genotyped or imputed) across two different genotyping platforms were tested for association with pyrexia in a hypothesis-free genome wide association approach. The *HLA* alleles (n=50) were stratified into a separate tier and analyzed for associations with pyrexia.
Data source: Clinical data was collected during the conduct of clinical studies BRF113710, BRF113929, BRF113683, MEK115306 and MEK116513.
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 primary PGx analysis population consisted of subjects enrolled in clinical studies BRF113710, BRF113929, BRF113683, MEK115306 or MEK116513 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). A pyrexia case was defined as any metastatic melanoma subject with normal temperature at baseline (< 38 ºC) and developing an AE of grade ≥2 pyrexia (>39 ºC) according to *NCI Common Terminology Criteria for Adverse Events* (CTCAE v.4.0) while receiving dabrafenib alone or in combination with trametinib. A pyrexia control was defined as a metastatic melanoma subject with normal temperature at baseline (< 38 ºC) and no fever despite sufficient exposure to dabrafenib or a combination of dabrafenib and trametinib (cumulative duration of exposure of at least 139-190 days across the clinical studies, corresponding to the time by which >90% of 'Cases' had an event of pyrexia). Of the 1031 subjects who consented for PGx research in the 5 clinical studies, 218 and 361subjects met the definition of

pyrexia case and control, respectively, and were selected for primary PGx analysis. A subset of pyrexia cases (n=136) who developed grade ≥2 pyrexia during the first 8 weeks of treatment with dabrafenib or dabrafenib + trametinib were selected for the secondary analysis of early onset pyrexia and were compared to the same controls as in the primary PGx population. The population for secondary analysis of time to pyrexia onset included all pyrexia cases (n=218) and all the subjects without a pyrexia event during the treatment period (n=580 across all the clinical studies). Melanoma subjects with grade 1 pyrexia (38-39 ºC; n=210 across studies) were excluded from all the primary and secondary analyses. Subjects from vemurafenib arm of MEK116513 (n=267) were also excluded from the analyses as vemurafenib treatment is not associated with pyrexia.

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, MEK115306 and MEK116513 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*. Time-to-pyrexia onset was defined as the number of study days from initiation of treatment until the first grade ≥2 pyrexia event. Subjects who did not have pyrexia were censored at the end of total cumulative days of study treatment for time to pyrexia onset analysis.

Data Analysis Methods: Genome wide associations with pyrexia or early onset pyrexia case-control status were conducted using logistic regression. Associations with time to pyrexia onset were conducted using Cox 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 $p \leq 0.05$ were included in the analysis model while testing for genetic effect. Melanoma subjects from the combination arm of MEK116513 were analyzed separately. Summary statistics from this and the clinical studies analyzed previously in 200997/PGx7550 (BRF113710, BRF113929, BRF113683 and 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 and tested for associations with all pyrexia endpoints (primary and secondary).

Limitations: With 218 pyrexia cases and 361 controls, there was >80% power to detect associations of common genome wide and *HLA* genetic variants (minor allele frequency (MAF) >5%) with effects (odds ratios (ORs)) greater than 5.8 and 3.2, respectively. However, there was limited power 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: No genome wide or *HLA* variant was significantly associated with pyrexia at pre-specified thresholds, assuming Bonferroni adjustment for multiple tests ($p<5.0e-08$ and $p<0.001$, respectively).Investigation of pyrexia in a subset of early onset pyrexia cases (secondary endpoint) also did not identify any significant associations. Investigation of time to pyrexia onset (secondary endpoint) identified association with an intergenic variant on chromosome 16 (rs141798568) just below the pre-specified multiple testing threshold ($p= 5.06e-08$). However, its functional significance could not be determined based on the available data in literature.

Conclusions: This study was well powered to detect relatively large effects. The lack of statistically significant associations for any of the 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.