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: GSK2251052

Study No.:LRS114689

Title: Study LRS114689: A study to assess the safety, tolerability and preliminary efficacy of GSK2251052 in the treatment of complicated intra-abdominal infection in adults

Rationale: Complicated intra-abdominal infections are among the most common infections in general surgery. Effective management of cIAIs includes early diagnosis, surgical intervention and antimicrobial therapy. The bacterial pathogens involved in cIAIs depend on the abdominal site of the origin of infection but include a wide variety of Gram-positive and Gram-negative aerobes and anaerobes, and are generally polymicrobial. GSK2251052 was not expected to be active against enteroccoci, staphylococci and some species of streptococci that may be isolated in this study from some subjects' source of infections; therefore concomitant use of vancomycin, at the discretion of the investigator was permitted. GSK2251052 demonstrated *in vitro* activity against *Enterobacteriaceae*, *P. aeruginosa* and against anaerobic pathogens including *Peptostrepococcus* spp., *B. fragilis*, *Bacteroides* spp, *Prevotella* spp and *Finegoldia magna*. GSK2251052 also demonstrated a favorable tolerability and pharmacokinetic profile; therefore, it was hypothesized that GSK2251052 would potentially be an effective treatment for patients with cIAI and may have had potential to offer clinical efficacy when these infections are the result of pathogens resistant to currently available therapies.

Phase: II

Study Period: 03-Oct-2011 – 05-Mar-2012

Study Design:

Prospective, randomized, multicenter, parallel group, active controlled, double-blind, double-dummy, multi-dose study of the safety, tolerability and efficacy of GSK2250152 compared to meropenem in the treatment of adult subjects with cIAI.

Duration of study: 30 to 42 days, with a minimum of 10 study visits:

- Baseline Visit 1 (Day 1), randomization
- On IV Therapy Visits (daily assessments while on IV therapy; Day 2-14).
- End of IV Therapy Visit (0-24 hours post-IV therapy)
- Hematology Safety Visit (2-4 days post-IV therapy)
- The duration between the Hematology Safety and the TOC visit may not be more than 5 days
- Test of Cure Visit (5-9 days post-IV therapy)
- Early Follow-up Safety Visit (14-17 days post-IV therapy)
- Late Follow-up Visit (21-28 days post-IV therapy)

Four subjects in the concurrent LRS114688 study, investigating the safety, tolerability, and efficacy of GSK2251052 therapy compared to imipenem-cilastatin in the treatment of adult subjects with febrile complicated lower urinary tract infections and acute pyelonephritis, were identified as having Gram-negative isolates with elevated minimum inhibitory concentration (MIC)s to GSK2251052. Three of these demonstrated a significant increase (>32-fold) in GSK2251502 MIC between their Baseline and Day 2 isolates.

Due to the resistance observed in Study LRS114688, Study LRS114689 was terminated with 15 subjects enrolled.

Centres: Five centres in four countries (U.S., Spain, France and Russia)

Indication: complicated Intra-abdominal Infection

Enrolment was monitored to ensure that no more that 30% of the total number of subjects to be enrolled were those with appendiceal perforations. Once the number of enrolled of subjects with appendiceal perforations neared the 30% threshold, sites were to be notified and enrolment to this group of subjects was to be closed.

Treatment:

Subjects randomized to GSK2251052:
GSK2251052 IV 750 or 1500 mg infused over 60 minutes BID plus three doses of meropenem placebo saline infused

over 30 minutes

Subjects randomized to meropenem:
Meropenem 1 g infused over 30 minutes TID plus two doses of GSK2251052 placebo saline solution infused over 60 minutes

Objectives:

Primary

- To evaluate the safety and tolerability of GSK2251052 in the treatment of adult subjects with complicated intra-abdominal infection (cIAI)
- To evaluate the clinical and microbiological efficacy of GSK2251052 in microbiologically evaluable adult subjects with cIAI

Secondary

- To compare the clinical and microbiological efficacy of GSK2251052 to meropenem in microbiologically evaluable adult subjects with cIAI
- To evaluate the pharmacokinetics of GSK2251052 and characterize the pharmacokinetic/pharmacodynamic (PK/PD) relationship in the study population

Primary Outcome/Efficacy Variable

Clinical response at the Test of Cure visit was the primary efficacy outcome

Safety outcome included evaluation of data from all adverse events (AEs) and serious adverse events (SAEs)

Secondary Outcome/Efficacy Variable(s):
PK Endpoints:

- maximum observed plasma concentration (Cmax)
- time to Cmax (tmax)
- area under the plasma concentration-time curve [AUC(0-t)]

Due to the early termination of the study, limited PK data was obtained and the planned pharmacokinetic and pharmacokinetic/pharmacodynamic analyses were not performed.

Statistical Methods:

The original sample size (210 subjects) was chosen based on feasibility. Because of the early termination of the study, a frequentist summary was conducted to summarize the efficacy endpoints for the three treatment groups. The 'once a failure always a failure' approach was applied to the clinical response programmatically. If a subject had a clinical failure at any visit, the clinical outcome/response was assigned to clinical failure at all subsequent visits, irrespective of the subject's attendance at the visit. If for any reason a subject's clinical outcome was "Unable to Determine", their clinical response was set to be 'clinical failure' programmatically. If a subject's clinical outcome was "Clinical Recurrence" at Test of Cure and Late Follow Up, their clinical response was set to be 'clinical failure' programmatically. No other efficacy analyses were performed.

Safety data was summarized descriptively for AEs and SAEs.

Available PK concentration data were to be plotted and compared to predicted data in healthy volunteers from a previously developed population pharmacokinetic model; however, due to the early termination of the study these analyses were not performed.

Study Population: Key inclusion criteria included the requirement for: subject post-op and required surgery within the last 24 hours prior to the first dose of study medication or required surgical intervention; evidence of intra-abdominal infection; abnormal white cell count plus one other clinical symptom as defined in the protocol; Gram negative organism(s) positive or suspected or failed a prior Gram-negative treatment regimen; subject required antibacterial

therapy for ≥7 days and surgical intervention for the diagnoses listed in the protocol; pre-operative with peritoneal findings suggestive of cIAI as listed in the protocol.

Key exclusion criteria included: subject known to have abdominal wall abscess, small bowel obstruction/ischemic bowel disease without perforation, traumatic bowel perforation with surgery within 12 hours, perforation of gastroduodenal ulcer with surgery within 24 hours, intra-abdominal processes in which the primary aetiology is not likely to be infectious, simple cholecysitis, gangrenous/suppurative cholecystitis without rupture/extension beyond gallbladder wall, simple appendicitis, acute suppurative cholangitis, infected necrotising pancreatitis/pancreatic abscess; subject not managed by staged abdominal repair/open abdominal technique; Gram positive/pathogen resistant to study antimicrobial agent; acute physiology and chronic health evaluation (APACHE) II score >20; moderate or severe renal impairment; subject not likely to survive 4 to 6 week study period; history of seizures/central nervous system (CNS) abnormality; required concomitant systemic antibacterial agents other than vancomycin; required probenecid/valproic acid medications; known/pre-existing severe hepatic disease; Baseline haemoglobin <10 g/dL, haematocrit <30% and/or reticulocyte >5%; neutropenia; platelet count <75000 cells/mm3; immunocompromised; subject had systemic antibacterial therapy for cIAI within 48 hours prior to first dose of investigational product (IP); history of moderate/severe hypersensitivity to meropenem or β-lactam antibiotics; prior GSK2251052 treatment; subject pregnant or nursing; subject may be compromised by drop in haemoglobin ≥2.5 g/dL.

Due to the resistance observed in Study LRS114688, Study LRS114689 was terminated with 15 subjects enrolled.

		GSK2251052 750 mg	**GSK2251052 1500 mg**	**Meropenem**
Number of Subjects		5	4	5
Randomised, N		5	5	5
Randomised but not treated		0	1	0
Completed, n (%)		5 (100)	3 (75)	5 (100)
Total Number Subjects Withdrawn, n (%)		0	1 (25)	0
Withdrawn due to Adverse Events, n (%)		0	1 (25)	0
Demographics				
N (ITT)		5	4	5
Females: Males		1:4	1:3	1:4
Mean Age, years (SD)		34.0 (15.05)	41.3 (13.65)	34.6 (10.3)
Race, n (%)				
African American/African		1 (20)	0	1 (20)
Central/South Asian		0	0	1 (20)
East Asian		0	1 (25)	0
White/Caucasian/European		4 (80)	3 (75)	3 (60)
Primary Efficacy Results:		**GSK2251052 750 mg N=4**	**GSK2251052 1500 mg N=2**	**Meropenem N=4**
Microbiologically Evaluable (ME)	Test of cure clinical success, n (%)	3 (75)	1 (50)	4 (100)
	Clinical failure, n (%)	1 (25)	1 (50)	0
Microbiological Intent to Treat (MITT)	Test of cure clinical success, n (%)	3 (75)	1 (50)	4 (100)
	Clinical failure, n (%)	1 (25)	1 (50)	0

- AEs were collected from the start of study treatment and until the follow up visit
- SAEs were collected from the time a subject consented to participate in the study up to and including any follow up contact

AEs that occurred in more than one subject in any group			
Preferred Term, n (%)	**GSK2251052 750 mg N=5**	**GSK2251052 1500 mg N=4**	**Meropenem N=5**
Pyrexia	0	2 (50)	1 (20)
Pelvic abscess	2 (40)	0	0
Abdominal abscess	0	2 (50)	0
All Serious Adverse Events			
Preferred Term, n (%) [number of subjects who had events considered "related"]	**GSK2251052 750 mg N=5**	**GSK2251052 1500 mg N=4**	**Meropenem N=5**
Abdominal abscess	0	2 (50) [0]	0
Pelvic abscess	1 (20) [0]	0	0
Blood creatinine increased	0	1 (25) [0]	0
Haemoglobin decreased	1 (20) [0]	0	0
Pancreatitis acute	1 (20) [0]	0	0
Bile duct stone	0	1 (25) [0]	0

Conclusion:
Due to the resistance observed in Study LRS114688, Study LRS114689 was terminated with 15 subjects enrolled. In Study LRS114689, no subjects demonstrated a significant (>4-fold) increase in GSK2251052 MIC between pathogens recovered at Baseline and those at post-Baseline visits.

For the MITT population, clinical success rates remained the same for each visit. A similar profile was observed in the ME population. However, only a limited number of post-therapy bacteriology specimens were obtained for analysis and together with the small number of subjects in each treatment group, any interpretation of the efficacy results or the potential for development of resistance to GSK2251052 in this study should be treated with caution.

A total of 78 GSK2251052 concentrations were available from 9 subjects (n=5 for 750 mg, n=4 for 1500 mg). Observed concentration data tended to fall below the median predicted value for healthy volunteers across the 12 hour dose interval.

Twelve subjects reported AEs. Diarrhoea and pyrexia were the most common AEs and were reported in 3 subjects each. No trends in SAEs were noted within GSK2251052 doses or across doses. No subjects died during the study.