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.:LRS114688

Title: A randomised, double-blind, dose-finding, multicentre study of 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

Rationale: A complicated UTI (cUTI) is an infection associated with a condition, such as a structural or functional abnormality of the genitourinary tract, or the presence of an underlying disease that interferes with host defence mechanisms, which increase the risks of acquiring infection or of failing therapy. Complicated UTIs are also frequently associated with the presence of a urinary catheter. Pyelonephritis is identified clinically by flank pain and/or costovertebral angle (CVA) tenderness and fever, and is often accompanied by nausea, vomiting, sweats and malaise. Gram-negative species account for approximately 60 to 80% of the bacterial spectrum of complicated and nosocomially acquired UTIs comprising of Escherichia coli, followed by *Klebsiella* spp., *Pseudomonas* spp., *Proteus* spp., *Enterobacter* spp. and *Citrobacter* spp.]. Gram-positive pathogens account for about 15 to 30% of the spectrum and comprise enterococci and staphylococci.

Treatment of cUTI depends on the severity of the illness and generally encompasses the following goals: (1) management of the urological abnormality, (2) antimicrobial therapy ensuring a rapid and effective response and also to prevent recurrence of the infection, and (3) supportive care when needed. To avoid the emergence of resistant strains, antibiotic therapy is generally guided by urine culture whenever possible. Empirical therapy is also sometimes necessary to treat cUTI and in these circumstances the antibacterial spectrum of the antibiotic agent should include the most relevant pathogens.

GSK 2251052 has demonstrated *in vitro* activity against Gram-negative pathogens commonly associated with complicated urinary tract infections such as the *Enterobacteriaceae* and *P. aeruginosa*. GSK2251052 has a spectrum of microbiological activity that includes the majority of the pathogens responsible for lower cUTI and pyelonephritis (complicated and uncomplicated). It was therefore hypothesized, that GSK2251052 would be an effective treatment for patients with lower cUTI or acute pyelonephritis. As GSK2251052 works through a novel mechanism, it may offer the potential of clinical efficacy when these infections are the result of pathogens resistant to currently available therapies.

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Phase: II

Study Period: 28-Jun-2011 – 06-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 imipenem/cilistatin in the treatment of adult subjects with febrile complicated lower urinary tract infections (cUTI) and acute pyelonephritis.

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)
- Haematology Safety Visit (2-4 days post-IV therapy)
- The duration between the Haematology Safety and the TOC visit was not to 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 with cUTI/acute pyelonephritis, were identified as having Gram-negative isolates following treatment with GSK2251052, with elevated minimum inhibitory concentration (MIC)s to GSK2251052. Three of these isolates demonstrated a significant increase (>32-fold) in GSK2251502 MIC between their Baseline and Day 2 isolates.

Due to the rapid resistance development observed in these four patients, the study was terminated as there was concern that these microbiological findings could lead to treatment failure and rapid clinical deterioration. A total of 25 subjects were enrolled.

Centres: Eight centres in three countries (U.S., Spain and Greece)

Indication: Febrile complicated urinary tract infection or acute pyelonephritis (complicated or uncomplicated)

Treatment: Subjects randomized to GSK2251052:
GSK2251052 IV 750 or 1500 mg infused over 60 minutes BID plus four doses of imipenem/cilastatin placebo saline infused over 20 to 30 minutes

Subjects randomized to imipenem/cilastatin:
Imipenem/cilistatin 1 g infused over 20 to 30 minutes QID plus two doses of GSK2251052 placebo saline solution infused over 60 minutes
Dosing for imipenem-cilastatin was also adjusted according to the subject's renal function and weight.

Objectives:
Primary:

- To evaluate the safety and tolerability of GSK2251052 in the treatment of adult subjects with lower complicated urinary tract infection (cUTI) and pyelonephritis (complicated and uncomplicated).
- To evaluate the clinical and microbiological efficacy of GSK2251052 in microbiologically evaluable adult subjects with lower cUTI and pyelonephritis (complicated and uncomplicated).

Secondary:

- To compare the clinical and microbiological efficacy of GSK2251052 to imipenem/cilastatin in microbiologically evaluable adult subjects with lower cUTI and acute pyelonephritis (complicated and uncomplicated).
- To evaluate the pharmacokinetics of GSK2251052 and to characterise the pharmacokinetic/pharmacodynamic relationship in this study population.

Primary Outcome/Efficacy Variable:
Safety outcome included evaluation of all adverse events (AEs) and serious adverse events (SAEs, laboratory parameters including haematology and clinical chemistry, vital signs and ECGs.

Secondary Outcome/Efficacy Variable(s):
Clinical, microbiological and therapeutic response at End of therapy and Late Follow-up,

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: however, due to the early termination of the study these analyses were not performed.

Study Population:

	GSK2251052 750 mg	**GSK2251052 1500 mg**	**Imipenem/ cilastatin**
Number of Subjects	6	8	6
Randomised, N	6	8	6
Randomised but not treated	0	0	0
Completed, n (%)	6 (100)	8 (100)	5 (83)
Total Number Subjects Withdrawn, n (%)	0	0	1 (17)
Withdrawn due to Adverse Events, n (%)	0	0	0
Demographics			
N (ITT)	6	8	6
Females: Males	3:3	4:4	3:3
Mean Age, years (SD)	55.7 (13.6)	50.4 (24.45)	48 (17.48)
Race, n (%)			

African American/African		0	1 (12.5)	0
Central/South Asian		0	1 (12.5)	1 (16.7)
East Asian		1 (16.7)	0	0
White/Caucasian/European		5 (83.3)	6 (75)	5 (83.3)
Primary Efficacy Results:		**GSK2251052 750 mg N=6**	**GSK2251052 1500 mg N=8**	**Imipenem/ cilastatin N=5**
Microbiologically Evaluable (ME)	Test of cure therapeutic success, n (%)	1 (20)	5 (62.5)	1 (50)
	Therapeutic failure, n (%)	4 (80)	3 (37.5)	1 (50)
Microbiological Intent to Treat (MITT)	Test of cure therapeutic success, n (%)	1 (16.7)	5 (62.5)	1 (20)
	Therapeutic failure, n (%)	5 (83.3)	3 (37.5)	5 (80)

- 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=6**	**GSK2251052 1500 mg N=8**	**Imipenem/ cilastatin N=6**
Nausea	0	2 (25)	1 (17)
Alanine aminotransferase increased	1 (17)	2 (25)	0
Dizziness	1 (17)	0)	2 (33)
Haemoglobin decreased	0	2 (25)	0
Headache	0	0	2 (33)
All Serious Adverse Events			
Preferred Term, n (%) [number of subjects who had events considered "related"]	**GSK2251052 750 mg N=6**	**GSK2251052 1500 mg N=8**	**Imipenem/ cilastatin N=6**
Aspiration bronchial	0	1 (13) [0]	0
Haemoglobin decreased	0	1 (13) [1]	0
Cardiac arrest	0	1 (13) [0]	0
Escherichia bacteraemia	0	1 (13) [1]	0
Pulmonary embolism	1 (17) [0]	0	0

Conclusion:

Treatment with GSK2251052 led to the emergence of resistance in four subjects, who were identified as having Gram-negative isolates with elevated MICs to GSK2251052. Three of these subjects demonstrated a significant increase (>32-fold) in GSK2251502 MIC between their Baseline and Day 2 isolates. As a result of this emergent resistance, the study was terminated early with only 20 subjects enrolled.

There was no statistical significant treatment difference in efficacy rates between GSK2251052 (750 and 1500 mg) and imipenem-cilastatin at Test of Cure visit. However, given the small numbers in each treatment group, interpretations should be treated with caution.

A total of 89 GSK2251052 concentrations were available from 13 subjects (n=6 for 750 mg; n=7 for 1500 mg). Observed concentration data tended to fall around the median value and within the 90% confidence interval predicted for healthy volunteers across the 12 hour dose interval.

Sixteen subjects (80%) reported AEs. Nausea, alanine aminotransferase increased and dizziness were the most commons 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. However, one subject (Subject 202) (Spain) died sixty days after the last dose of investigational product due to aspiration bronchopneumonia and cardiac arrest.