2 SYNOPSIS

SPONSOR:	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.	
COMPOUND NAME:	Not applicable	
INDICATION:	Invasive fungal infections and suspected fungal-related febrile episodes in patients affected with newly diagnosed hematological malignancies (acute myeloid leukemia or acute lymphoid leukemia)	
PROTOCOL TITLE:	A non-interventional, multicentre, prospective study to estimate the incidence of invasive fungal infections and to monitor the diagnostic and therapeutic management of suspected fungal-related febrile episodes in patients affected with hematological neoplasm (Hema e-Chart II)	
TRIAL IDENTIFIERS:	Protocol Number:	803-01
	Clinical Phase:	Observational study
	EudraCT Number:	Not applicable
ETHICS:	This trial was conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research. For trial audit information see [16.1.8]. The signature of the primary/coordinating investigator is in [16.1.5.1] and the signatures of the principal authors of this report are in [16.1.5.2].	
TRIAL CENTERS:	This trial was conducted at 25 trial centers in Italy. A list of investigators and trial centers is provided in [16.1.3; 16.1.4].	
DESIGN:	For additional information about trial design, see the protocol in [16.1.1.1]. Sample case report forms are in [16.1.2].	
	Planned duration of main phase: Planned duration of run-in phase: Planned duration of extension phase:	not applicable not applicable not applicable
Objectives	<u>Primary objective:</u> 1) To estimate the rate of occurrence of possible, probable and proven invasive fungal diseases. <u>Secondary objectives:</u> 1) To prospectively monitor diagnostic and therapeutic actions in the management of hematological patients with suspected fungal-related febrile events (FEs). 2) To estimate the rate of deaths in patients with suspected fungal - related FEs.	

	3) To assess the outcome of patients with invasive fungal disease (IFD).4) To analyze the outcome of patients with suspected fungal-related FEs who receive either empirical or pre-emptive antifungal strategy. 5) To evaluate the economic burden related to healthcare resources utilization and cost for possible, probable and proven invasive fungal disease or with suspected fungal-related febrile events in hematological patients.	
Hypotheses	This was an observational study. Therefore neither formal statistical hypothesis was tested nor formal inferential statistical analysis of the study results was planned; only descriptive statistics was done.	
Treatment groups	Not applicable	

Endpoints and definitions	Primary endpoint		1) Rate of occurrence of possible, probable and proven invasive fungal diseases
	Secondary endpoints		1) Diagnostic and therapeutic actions in the management of hematological patients with suspected fungal-related FEs. 2) Rate of deaths in patients with suspected fungal-related FEs. 3) Outcome of patients with IFD. 4) Outcome of patients with suspected fungal-related FEs who receive either empirical or pre-emptive antifungal strategy. 5) Economic burden related to healthcare resources utilization and cost for possible, probable and proven invasive fungal disease or with suspected fungal-related febrile events in hematological patients.
Database lock	27-SEP-2016	Trial status	*24-FEB-2015* first subject first visit *21-JUN-2016* last subject last visit

RESULTS AND ANALYSIS:	This observational study evaluated 451 adult patients admitted to hematology wards to receive treatment for newly diagnosed hematological malignancies, with the aim to estimate the incidence of invasive fungal infections and to monitor the diagnostic and therapeutic management of suspected fungal-related febrile episodes. More than three quarters of patients (76.9%) presented at least one febrile event; overall, 650 febrile events were recorded, 7.4% of them (48 events) were invasive fungal infections, with level of certainty proven (18.75%), probable (37.5%) and possible (43.75%). First line antifungal therapy was administered in 190 febrile events (29.2%) (mostly amphotericin B liposomial, caspofungin and posaconazole). The first line antifungal therapy strategies were: empirical therapy (80%), pre-emptive therapy (18.4%) and targeted therapy (1.6%); the first line antifungal therapy response was: complete response (32.1%), stable disease (11.6%), partial response (11.1%), progression (5.3%). 46 febrile events (24.2%) were treated with following antifungal therapy after first line therapy: in 7 of these events, antifungal therapy was changed again after the first change. The rate of deaths for the 347 patients who presented at least one febrile event was 12.7%; the most frequent reasons for death were infection and haematological disease. The outcome of the 48 febrile events with diagnosis of invasive fungal disease was: at Week 4, partial response (45.8%), stable disease/progression (25%), complete response (10.4%), death due to other cause (10.4%), death due to IFI (6.3%); at Week 12, complete response (31.3%), partial response (31.3%), death due to other cause (22.9%), death due to IFI (6.3%), stable disease/progression (2.1%). The outcome of the 190 febrile events treated with first line antifungal therapy was: resolution of fever (92.1%), recovery from severe neutropenia (53.7%), increase beyond normal range in GPT (22.6%), GOT (15.8%) and creatinine (12.1%). This outcome did not differ substantially in patients receiving empirical therapy and pre-emptive therapy. The mean duration of therapies for febrile events was 12.77 days for antibiotic therapy, 10.48 days for antiviral therapy, 9.61 days for first line antifungal therapy and 9.58 days for following antifungal therapy. Additional analyses stratified according to hematological diagnosis, acute myeloid leukemia (AML, 367 patients) or acute lymphoid leukemia (ALL, 84 patients), have been performed with exploratory purpose.

	Out of the 650 febrile events reported, 571 were recorded in patients with AML and 79 in patients with ALL. Invasive fungal infections were reported in 38 febrile events (6.7%) in patients with AML and in 10 febrile events (12.7%) in patients with ALL. In patients with AML, the level of certainty of the 38 febrile events with diagnosis of invasive fungal infection was: proven (18.4%), probable (31.6%) and possible (50%). In patients with ALL, the level of certainty of the 10 febrile events with diagnosis of invasive fungal infection was: proven (20%), probable (60%) and possible (20%). First line antifungal therapy was administered in 165 febrile events in patients with AML (28.9%) and in 25 febrile events in patients with ALL (31.6%). In patients with AML, out of 165 febrile events treated with first line antifungal therapy, 38 events (23%) were treated with following antifungal therapy after first line therapy. In patients with ALL, out of 25 febrile events treated with first line antifungal therapy, 8 events (32%) were treated with following antifungal therapy after first line therapy. Overall, 297 patients (80.9%) with AML and 50 patients (59.5%) with ALL presented at least one febrile event. The rate of deaths was 14.1% for patients with AML and 4% for patients with ALL. The most frequent reasons for death were infection and haematological disease. The outcome at Week 4 of the febrile events with diagnosis of invasive fungal disease was mainly partial response (39.5%) and stable disease/progression (26.3%) for AML patients, partial response (70%) and stable disease/progression (20%) for ALL patients; the outcome at Week 12 was mainly complete response (31.6%) and partial response (28.9%) for AML patients, partial response (40%) and complete response (30%) for ALL patients. The outcome of the 165 febrile events in patients with AML who received first line antifungal therapy was: resolution of fever (90.9%), recovery from severe neutropenia (53.3%), increase beyond normal range in GPT (18.8%), GOT (13.9%) and creatinine (13.9%). The outcome of the 25 febrile events in patients with ALL who received first line antifungal therapy was: resolution of fever (100%), recovery from severe neutropenia (56%), increase beyond normal range in GPT (48%) and GOT (28%). The mean duration of therapies for febrile events was similar in the two groups of patients for antibiotic therapy (12.80 days vs 12.58 days), antiviral therapy (10.89 days vs 8 days), first line antifungal therapy (9.55 days vs 9.96 days) and following antifungal therapy (9.16 days vs 11.67 days). Being an observational study not requiring the administration of any

	therapeutic agent or specific procedures, safety data were not recorded and analyzed. The Statistical Analysis Plan is provided in [16.1.9].

Analysis description	**Primary Analysis**
Analysis population and time point description	The whole sample has been analyzed, according to the availability of data.
Summary	The rates of occurrence of possible, probable and proven invasive fungal diseases were estimated as the relative frequencies. The confidence intervals at 95% level have been computed using the Clopper-Pearson method.

Analysis description	**Secondary Analysis**
Analysis population and time point description	The same as for primary analysis
Summary	The therapeutic actions in the management of hematological patients with suspected fungal-related febrile events were examined by estimating frequency and percent of patients to whom each therapy was administered. The diagnostic actions were described by mean number of exams performed for each febrile event, together with the absolute frequency and percentage of positive diagnosis. The rate of deaths in patients with suspected fungal-related FEs were estimated as the relative frequencies, together with 95% Clopper-Pearson confidence itervals. The outcome of patients with IFD was assessed by relative frequencies of each possible outcome at 4 and 12 weeks of follow-up, together with the exact confidence intervals at 95% level (Clopper-Pearson method). The outcome of patients with suspected fungal-related FEs who receive either empirical or pre-emptive antifungal strategy (at first line) was studied by relative frequencies of each possible outcome, separately for the two groups of patients. The healthcare resources utilization for possible, probable and proven invasive fungal disease or with suspected fungal-related febrile events in hematological patients were evaluated for the whole sample and according to the level of certainty of IFI as descriptive statistics regarding duration of therapies and number of diagnostic exams.

CONCLUSIONS:	This observational study collected data on 451 adult patients admitted to hematology wards to receive treatment for newly diagnosed hematological malignancies. More than three quarters of patients (76.9%) presented at least one febrile event; overall, 650 febrile events were recorded, 7.4% of them (48 events) were invasive fungal infections: proven (18.75%), probable (37.5%) and possible (43.75%). First line antifungal therapy was administered in 190 febrile events (29.2%). The first line antifungal therapy strategy was mostly empirical therapy (80%) and the response was complete response in 32.1% of febrile events, stable disease in 11.6% and partial response in 11.1%. About a quarter of the 190 febrile events treated with first line antifungal therapy (24.2%) were treated with following antifungal therapy after first line therapy; in 7 of these events, antifungal therapy was changed again after the first change. The rate of deaths for the 347 patients who presented at least one febrile event was 12.7%; the most frequent reasons for death were infection and haematological disease. The outcome of the 48 febrile events with diagnosis of invasive fungal disease was: at Week 4, partial response (45.8%), stable disease/progression (25%), complete response (10.4%), death due to other cause (10.4%), death due to IFI (6.3%); at Week 12, complete response (31.3%), partial response (31.3%), death due to other cause (22.9%), death due to IFI (6.3%), stable disease/progression (2.1%). With regard to the outcome of the 190 febrile events treated with first line antifungal therapy, resolution of fever was achieved in 92.1% of febrile events, recovery from severe neutropenia in 53.7%, an increase beyond normal range was observed for GPT (22.6%), GOT (15.8%) and creatinine (12.1%). This outcome did not differ substantially in patients receiving empirical therapy and pre-emptive therapy. The mean duration of therapy for febrile events was shorter for first line antifungal therapy (9.61 days) and following antifungal therapy (9.58 days) than for antibiotic therapy (12.77 days) and antiviral therapy (10.48 days). Additional analyses stratified according to hematological diagnosis, acute myeloid leukemia (AML, 367 patients) or acute lymphoid leukemia (ALL, 84 patients), have been performed with exploratory purpose. Out of the 650 febrile events reported, 571 were recorded in patients with AML and 79 in patients with ALL. A lower rate of occurrence of invasive fungal infections was reported in patients with AML

	than in those with ALL: 38 febrile events (6.7%) in AML patients (with level of certainty: proven, 18.4%, probable, 31.6%, and possible, 50%) and 10 febrile events (12.7%) in ALL patients (with level of certainty: proven, 20%, probable, 60%, and possible, 20%). Antifungal therapy was administered more frequently in patients with ALL than in those with AML: first line antifungal therapy was administered in 28.9% of febrile events in patients with AML and in 31.6% in patients with ALL; following antifungal therapy in 23% of febrile events in patients with AML and in 32% of febrile events in patients with ALL. Overall, 297 patients (80.9%) with AML and 50 patients (59.5%) with ALL presented at least one febrile event. The rate of deaths was higher for patients with AML (14.1%) than for patients with ALL (4%). The most frequent reasons for death were infection and haematological disease. The outcome at Week 4 of the febrile events with diagnosis of invasive fungal disease was mainly partial response (39.5%) and stable disease/progression (26.3%) for AML patients, partial response (70%) and stable disease/progression (20%) for ALL patients; the outcome at Week 12 was mainly complete response (31.6%) and partial response (28.9%) for AML patients, partial response (40%) and complete response (30%) for ALL patients. With regard to the outcome of febrile events treated with first line antifungal therapy, resolution of fever was obtained in 90.9% of AML patients and 100% of ALL patients, recovery from severe neutropenia in about half patients in both groups of patients, a higher increase beyond normal range in GPT and GOT was observed in ALL patients, an increase in creatinine only in AML patients. The mean duration of therapies for febrile events was similar in the two groups of patients for antibiotic, antiviral, first line antifungal and following antifungal therapy. Being an observational study not requiring the administration of any therapeutic agent or specific procedures, safety data were not recorded and analyzed.
PUBLICATION(S):	Publications are in [16.1.1.11].
REPORT DATE:	22-Mar-2017