

Ketek Fact Chronology

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Date & Time	Reg TL	3014 TL	Fact Text	Source(s)	Unresolved
Wed 02/18/1998	✓		Aventis opens IND #55,283, which eventually gives rise to NDA 21-144 for Ketek in four indications: Community acquired pneumonia (CAP); Acute Sinusitis (AS); Acute Exacerbation of Chronic Bronchitis (AECB) and Tonsillopharyngitis (T/P).	Ketek Timeline (C) from CDER	
Mon 02/28/2000	✓		Aventis submits original NDA 21-144 for CAP, AS, AECB and T/P. Review reveals one patient with apparent drug-induced hepatotoxicity (confirmed on liver biopsy). Review at AFIP shows marked similarities to trovafloxacin (Trovan) hepatotoxicity	Ketek Timeline (C) from CDER; 4/26/01 AIDAC Meeting Minutes	
Wed 02/28/2001	✓		Aventis submits a Major Amendment to 21-144 to address the issue of a resistance claim for PCN-resistant S. Pneumoniae and ECN-resistant S. Pneumoniae.	Ketek Timeline (C) from CDER;	
Thu 04/26/2001	✓		AIDAC meeting. Aventis presents efficacy data; FDA presents toxicity data. Significant concerns: only 3200 patients received Ketek in Phase III trials; Q-T prolongation and 3 hepatitis cases as AEs. AC notes insufficient data to consider Tonsillopharyngitis as an indication; votes not to approve Ketek for AS and AECB as other low-risk therapeutics are available; votes to approve for CAP but based on toxicity data, AC recommends FDA require a large safety study be conducted in lieu of multiple warnings and distribution restrictions.	AIDAC Meeting Transcripts	
Fri 06/01/2001	✓		FDA issues an "approvable letter" to NDA 21-144 for three indications, CAP, AS, and AECB, but states submitted data are insufficient. States "It would be helpful" for Aventis to perform a large safety study, among	FDA Meeting minutes, 12/19/02; Approval letter in ROI #5, Atch XXX.	

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**	**	**	other things.	**	**
Tue 09/18/2001	✓	✓	MEETING between CDER and Aventis to discuss the design of Study3014.	Ketek Timeline (C) from CDER;	
Fri 10/12/2001	✓		MEETING between CDER and Aventis to discuss the deficiencies enumerated in 6/1/01 "Approvable" letter and clinical trials sponsor would perform to address them.	Ketek Timeline (C) from CDER;	
Fri 10/19/2001 - Tue 05/14/2002	✓	✓	Aventis conducts Study3014, enrolling 24,562 patients at 1824 sites in the US. 12,277 were randomized to the Ketek arm; 12,161 received Ketek and 12,159 were evaluable for safety purposes. Of those, 2807 (23.1%) reported AEs, which was comparable to the AMC arm (2745 (22.9%) of 11,978 patients).	Study3014 Disk 1, 3014.pdf, P. 1-7	
Wed 10/31/2001		✓	Kirkman-Campbell is initiated into Study3014 by telephone	PPD Interim Monitoring Report,	
Thu 11/29/2001		✓	First monitoring visit conducted at Kirkman-Campbell's site. 65 subjects enrolled; deficiencies included dating of PI's signature on study docs (CRFs, ICFs and Labs?).	Khosla e-mails	
Mon 12/03/2001		✓	PPD e-mails Aventis' Grethe that Kirkman-Campbell will be at 100 subjects enrolled by the end of the day and asks whether there is a limit to the number of patients that can be enrolled at a single site. Grethe asks Stager, who opines that enrollment can continue to at least 500. PPD then sets the limit on the number of subjects enrolled to 500 per site.	PPD e-mails File	
Thu 01/17/2002		✓	THROUGH 1/18/02: Aventis (Khosla) conducts a GCP QA audit at Kirkman-Campbell's site and finds date, consent form issues that need corrective actions.	Khosla e-mails	
Tue 01/22/2002		✓	First reference to	Grethe TREAT	

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**	**	**	numerous patients in rapid succession and while the office is closed to patients.	**	**
Wed 02/20/2002 6:48 p.m. ET		✓	Reynolds e-mails Tropmann again, forwarding a spreadsheet that discloses abnormal randomization at Kirkman-Campbell site.	ROI #1, Atch 1	
Thu 02/21/2002		✓	PPD faxes a copy of the study monitor notes from Kirkman-Campbell's site to Khosla at Aventis	ROI #5, Atch XXX, Fax cover sheet (Box DSI 1)	
Fri 02/22/2002		✓	Aventis decides to analyze all of the lab data from Kirkman-Campbell's site.	Grethe's TREAT Meeting minutes, 2/22/02	
Mon 02/25/2002 9:13 a.m. ET		✓	Grethe forwards Reynolds' first message about suspicions at Kirkman-Campbell to Stager. It is not clear how she got Reynolds' original e-mail, which was address only to PPD personnel.	ROI #1, Atch 1	
Mon 02/25/2002 4:22 p.m. ET		✓	Stager responds in an e-mail to Grethe stating he finds nothing unusual about the data. Grethe sends Stager's message to Tropmann.	ROI #1, Atch 1	
Mon 02/25/2002 5:36 p.m. ET		✓	Reynolds e-mail Grethe directly, notifying her about the incidence of lab reports being duplicative and the high randomization rates at Kirkman-Campbell's site.	ROI #1, Atch 1	
Tue 02/26/2002		✓	Aventis decides the methodology to use when reviewing a "site with a large number of patients" is to look at variability in lab data drawn on the same day to ensure it is not less than expected.	Grethe's TREAT Meeting minutes, 2/26/02	
Wed 02/27/2002		✓	Randy Anderson, from PPD HQs in Wilmington, NC, asks PPD's biostatistics department whether they can assist in "investigating some potentially fraudulent trends in some Phase IV study data.	PPD e-mails file	

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Wed 02/27/2002 10:05 a.m. ET		✓	Tropmann e-mails PPD employee Dunlap requesting PPD's biostatistical department look at the data from Kirkman-Campbell's site because she was afraid Aventis' Bill Stager wouldn't look at it.	ROI #2, Attachment 4	
Wed 02/27/2002 3:15 p.m. ET		✓	Lasley e-mails Grethe and her supervisor, Khosla, requesting a teleconference listing their findings at the Kirkman-Campbell site which concern them. They include a summary of their findings and offer to fax over specific examples before the teleconference. Grethe responds at 4:46 p.m. stating it would depend on Khosla's schedule as he is traveling.	ROI #2, Atch 5	
Wed 02/27/2002 7:02 p.m. ET		✓	Grethe e-mails Khosla that they should talk talk about the Kirkman-Campbell site, but "could we please be careful how we disseminate information on this site until we do. By then we will also have Bill's (Stager's) final analysis on the lab values. I just don't want people panicking until there is a need to do so."	ROI #2, Attachment 6	
Wed 02/27/2002 8:32 p.m. ET		✓	(7:32 Mexican Time Zone) Khosla e-mails Grethe to set up a teleconference between PPD and Aventis early in the week of March 4, 2002.	ROI #2, Attachment 6	
Fri 03/01/2002		✓	Reynolds prepares a seven page list of lab results from Kirkman-Campbell's site that appear to be tests run on same samples for different patients.	PPD e-mails File	
Mon 03/04/2002		✓	Aventis and PPD conduct a teleconference to discuss data irregularities at Kirkman-Campbell's site. Attendees were: (PPD) McCormick, Reynolds, Lasley, Edwards, plus two CRAs. (Aventis) Grethe, Shoemaker, plus others. Due to confidentiality agreement, the	ROI #2, p. 3; McCormick 6/12/06 MOI p. 1.; Aventis Briefing document BD-00042, Pg. 6 in HOT DOCS FILE	

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**	**	**	contents of the call cannot be divulged w/o GJ subpoena. The upshot of the meeting is that Aventis says it will take over monitoring the Kirkman-Campbell site.	**	**
Tue 03/05/2002		✓	Stager is directed to do additional statistical analysis of the data from Kirkman-Campbell's site, following which an "action plan" will be drawn up at Aventis.	Grethe's TREAT Meeting minutes, 3/5/02	
Wed 03/06/2002 10:24 a.m. ET		✓	PPD CRA Sonia Pal e-mails other PPD CRAs, which is forwarded to Tropmann, concerning her findings of an audit at Kirkman-Campbell's site. She observed ink irregularities, significant lack of AEs in first 360 patients and AEs added post hoc in files relating to patients 361-402.	ROI #1, Atch 1	Tropmann: Did you forward this info to Aventis? Who at Aventis?
Fri 03/08/2002		✓	"Site manager" (NFI) had a discussion with Kirkman-Campbell's site about the lack of AEs and discovered the site did not know the AE reporting requirements. Decision is made that Grethe will go on next monitoring visit.	Grethe's TREAT Meeting minutes, 3/8/02	
Mon 03/11/2002	✓		MEETING between CDER and Aventis to discuss the resubmission content and format.	Ketek Timeline (C) from CDER;	
Thu 03/14/2002		✓	Stager completes his analysis of suspicious lab data found at Kirkman-Campbell's site, concluding that her results are similar to the two next highest enrolling PI sites.	Aventis Briefing Document DB-00042, page 6; HOT DOCS FILE	
Thu 03/14/2002 5:10 p.m. ET		✓	Reynolds e-mails four PPD CRAs, including the summary of his biostatistical analysis of data from Kirkman-Campbell's site that shows she had a higher incidence of LFT changes than would be typical and that similar findings were produced by data that were collected at site # 0096 (PI = Carl Lang).	ROI #1, Atch 1	FU w/Lang Data

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Fri 03/15/2002		✓	A cryptic entry in the TREAT Meeting Minutes's QA section reads: Couple questions on behalf of Aventis QA. FU Letter - submitted to Melinda [Edwards] yesterday. She will review and fax to Ranjan Monday.	Grethe's TREAT Meeting minutes, 3/15/02	Khosla and Grethe: Why was the forged signature issue kept out of the follow-up letter?
Tue 03/19/2002		✓	Aventis allegedly has a follow-up meeting at which QA is briefed on Stager's statistical analysis of Kirkman-Campbell's lab data and "collectively decide" to keep the data in the Study.	Grethe 2/25/03 MOI; 7/03 Aventis briefing doc	Who was in charge, and did this precede enrollment closure?
Tue 03/19/2002 1:22 p.m. ET		✓	McCormick responds to Cisneros' earlier e-mail containing a draft follow-up letter regarding her audit of Kirkman-Campbell's site. Cisneros said that Khosla, Shoemaker and Aschenbrenner wanted to keep the "forged consent issue" out of the follow-up letter. McCormick responded that he did not agree with Aventis' decision and instructs Cisneros to retain the documentation and "clearly document that Aventis required the removal from the follow-up letter."	ROI #2, Attachment 7	
Thu 03/21/2002		✓	PPD conducts a close-out and for-cause monitoring of McLeod's site. The PI failed to get any informed consents and had (among 30 randomized patients) reported fewer than 3 AEs.	DSI Box #5, McLeod Monitoring Report	
Mon 04/01/2002		✓	THROUGH APRIL 5. Third monitoring visit of Kirkman-Campbell's site conducted. New deficiencies included enrolling subjects with PCN/ERY allergy, new antibiotic therapy noted and DCF generated. Nadine Grethe participates in the monitoring on April 4 and 5 (Thursday and Friday). The meeting minutes for the next two TREAT meetings are missing.	Khosla e-mails; TREAT Meeting minutes, 3/22/02 and 4/2/02.	Interview Grethe

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Mon 04/08/2002		✓	THROUGH 4/12. PPD conducts a close-out monitoring of Sghiatti site, finds numerous GCP, informed consent problems; no CRFs are signed, no lab reports are signed by PI. PI enrolled two of his staff members.	Sghiatti Monitoring file, DSI Box #5	
Tue 04/16/2002		✓	TREAT Meeting minutes's QA entry: "Kirkman-Campbell - Will use memo to files that she signed when we were there as a letter to file. Subject 249 VJS - will decide what to do with this patient after we receive information from the site.	Grethe's TREAT Meeting minutes, 4/16/02	
Tue 04/23/2002		✓	Aventis completes audit report of Kirkman-Campbell's site.		
Wed 05/22/2002		✓	Aventis locks the database of Study3014.	Study3014 CSR p. 103	
Fri 05/24/2002		✓	PPD employee Melinda Edwards e-mails Ranjan Khosla that Dr. Vincent Sghiatti's site was inspected April 8 - 12, 2002, following his earlier refusal to allow monitors at site. Discrepancies noted include no drug accountability log; dosing discrepancies; low adverse event rate; loss of investigational product; PI did not sign any CRFs or lab reports and two missing CRFs.	Khosla e-mails;	Khosla / Edwards FU questions.
Mon 06/03/2002		✓	THROUGH 6/4. PPD conducts second close-out inspection at Sghiatti's site. Finds many previously identified problems still exist and continuing failure to adhere to protocol.	Sghiatti Monitoring file, DSI Box #4	
Wed 06/05/2002		✓	PPD Employee Joyce Vito faxes memo to Kirkman-Campbell stating Study Subject # 249's informed consent signature appears to have been forged by the study coordinator. Kirkman-Campbell is instructed to have the patient re-consented and document it on a memo to file.	ROI #5, Attach	
Wed 06/05/2002		✓	Khosla responds to Edwards	Khosla e-mails;	Khosla /

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12:17 p.m. ET	**	**	5/24/02 e-mail stating in part, "Thank you very much for confirming that no doubt exists regarding the reliability of the data from this site, and no misconduct could be suspected."	**	Edwards FU questions.
Mon 06/10/2002		✓	Aventis' deadline for correcting data.	Study3014 CSR pg 103	
Thu 07/11/2002			PPD's Vito gives up trying to get Kirkman-Campbell to finish the monitoring visit close-outs.	BD-07288	
Wed 07/24/2002	✓	✓	Aventis re-submits NDA 21-144, which includes Study3014 and foreign post-marketing data. The study itself is signed by Nusrat as Study Director; Grethe as Study Coordinator and Stager as Study Biostatistician.	FDA Meeting minutes, 12/19/02; Study3014 disks	
Fri 10/04/2002	✓	✓	Khosla e-mails Aventis and Tropmann that FDA will inspect Kirkman-Campbell's site on 10/15/02; requests PPD send two CRAs to assist him and Aschenbrenner on 10/08/02 in preparing for the inspection.	Khosla e-mails	
Tue 10/15/2002	✓	✓	FDA inspection of Kirkman-Campbell's site begins.	Khosla e-mails	
Wed 10/16/2002		✓	Kirkman-Campbell e-mails Khosla and updates him about the FDA inspection; says she's "most anxious." Asks what "our" appropriate response should be regarding the existence of additional antibiotics.	Khosla e-mails	
Sun 10/20/2002		✓	Kirkman-Campbell e-mails Khosla and updates him about the FDA inspection, which is now over.	Khosla e-mails	
Tue 10/22/2002		✓	Snedeker e-mails Khosla asking for a time when Kirkman-Campbell can telephonically brief him on the FDA inspection.	Khosla e-mails	
Tue 10/22/2002	✓	✓	OCI's SA West contacts Kirkman-Campbell seeking an interview. He advises her he has opened a criminal investigation into her conduct	West ROI #1, Pg. 2	

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**	**	**	during Study3014.	**	**
Thu 10/24/2002		✓	Bryers e-mails instructions to the Ketek study team, including Shoemaker, Nusrat, Stager and Grethe, to "Work with QA-GCP to support the investigator replies to 483."	Khosla e-mails; ROI #5, Atch XXX.	
Fri 10/25/2002		✓	Shoemaker responds by e-mail to Bryers with a report on the problems at Kirkman-Campbell's site. Under the heading, "Was appropriate action taken?" Shoemaker states, "Following notification of February monitoring findings, deficiencies noted were addressed directly to the investigator site and a description and explanation was documented in the investigator study file and/or chart. Deficiencies involving protocol violation were notified to the IRB. The lab values were evaluated internally by the study team and concluded there were no unexpected patterns detected in the values reported. Though numerous deficiencies were found, no known deficiencies were interpreted to conclude that patients did not exist, were not consented, did not receive drug and were not evaluated per protocol with the exception of noted protocol violations. As such, no action was taken to censor data in the report."	Khosla e-mails; ROI #5, Atch XXX.	
Sun 11/17/2002		✓	Kirkman-Campbell e-mails Khosla thanking him for his assistance in replying to the 483.	Khosla e-mails	
Tue 12/10/2002	✓	✓	DSI learns that Dr. Knect's site in Oklahoma had significant data integrity issues and had enrolled 2.5% of the town's population, including his relatives. However, there is "not enough time" to issue an assignment before (something) and perhaps the site should be inspected post-PDUFA.	Brenda Friend e-mails in Ekay's e-mail folder	FU w/ these PI's data

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Wed 12/18/2002	✓	✓	Shoemaker, Nusrat and Grethe all discuss via e-mail preparing an on-site monitoring briefing, with particular reference to Kirkman-Campbell's site.	Briefing Doc p 02415	
Thu 12/19/2002	✓		Meeting between CDER/ODE and Aventis held at sponsor's request. Firm wanted to provide the Agency with data and slides it would provide to the AIDAC meeting on 1/8/03. FDA tells Aventis it is concerned with poor monitoring of Study3014 and two site inspections revealed significant fraud indicators. Aventis "pointed to difficulties w/ F/U on reported irregularities, considering the fast enrollment achieved during the trial. Aventis indicated that when it became aware of irregularities at the Kirkman-Campbell site, her participation was discontinued. Aventis did not explain why her data were included in the study nor why FDA was not informed of data integrity issues. Aventis rationalized ineligible patients as not important because Study 3014 was a safety study, not an efficacy study	ROI #1, Pg2; FDA Meeting minutes	
Thu 12/19/2002	✓	✓	DSI inspects Dr.Egisto Salerno, Site #1057, the third highest enroller in Study3014. Although a 483 issues, DSI later opines that the data arising from that site are still reliable.	Ketek Timeline (C) from CDER;	
Mon 12/30/2002	✓	✓	DSI inspects Dr. Carl Lang, Buffalo Grove, IL, Site #96, Study3014's second highest enroller with 251 patients. Discovers a total of 40 clin labs not done and insufficient documentation regarding eligibility.	Ketek Timeline (C) from CDER;	
Wed 01/08/2003	✓	✓	AIDAC meeting. Aventis provides AC with Study3014 without any mention of data integrity issues. Aventis also provides AC with European post-marketing that exceeds	AIDAC Meeting Transcripts.	

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**	**	**	what has been provided to the FDA. Committee votes to recommend approval.	**	**
Tue 01/21/2003	✓	✓	DSI advises DAIDP in writing that inspections at the top three enrolling sites in Study3014 revealed significant issues at each site and 483s were issued to each PI.	AIDAC Meeting 3-A, 12/14/06, transcript page 122.	
Fri 01/24/2003	✓	✓	FDA issues approvable letter to Aventis for CAP, AECB and AS, but denies final approval based on "remaining questions about the safety" of Ketek. FDA questioned the validity of Study3014's results and found Aventis' post-marketing data were incomplete. Complete Phase IV data from overseas and an audit of Study3014 are requested to "assess overall data integrity and to determine what role Study3014 can have in support of your marketing application...".	Approvable Letter in NDA Correspondence file	
Wed 02/19/2003	✓		At a regulatory briefing, virtually every executive in CDER learns that three DSI inspections suggest Study3014's data lack integrity. Decisions = more inspections to determine if Study3014 can be used to support NDA and if not, the division might be able to rely upon foreign post-marketing data. Wrt adverse events, executives agreed with DAIDP that hepatic and cardiac AEs appear consistent with other currently marketed antibiotics, and Study3014 does not appear to be critical to reaching this conclusion. Some members agreed that the results of an investigation into Study3014 may not be critical for approval of some of the proposed indications.	Meeting Minutes	
Mon 02/24/2003			OCI Agent West interviews Aschenbrenner at Aventis' office with corporate counsel present.	Aschenbrenner MOI	

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Tue 02/25/2003			OCI Agent West interviews Khosla at Aventis, with corporate counsel present	Khosla MOI	
Tue 02/25/2003			OCI Agent West interviews Marini at Aventis, with corporate counsel present	Marini MOI	
Tue 02/25/2003			OCI Agent West interviews Grethe at Aventis' office with corporate counsel present.	Grethe MOI	
Fri 02/28/2003	✓	✓	CDER/DAIDP and Aventis meet to discuss FDA's 1/24/03 Approvable letter and the question, 'Whether the agency can reasonably rely on the integrity of Study3014 safety data submitted in Amendment 2.' Meeting minutes by FDA suggest Aventis did not believe the discrepancies surfaced by monitoring and audits Aventis reflected significant GCP deviations, though Aventis responded that it was concerned about the Lang, Kirkman-Campbell and Salerno sites. It just did not think the concerns invalidated the data produced at the sites given the intent of the study, which was to assess the safety of telithromycin.	Pg 2 of cover letter, Disk "NDA 21144 Letter Date 7/3/03."; Aventis' 5/16/03 response to FDA meeting minutes.	Obtain FDA meeting minutes
03/??/2003	✓	✓	DSI analysis of Study3014 reveals 19 sites enrolled abnormally large percentage of adults (>1%) in catchment area.	Ross Timeline	FU w/ these Pls data
03/??/2003	✓	✓	DSI visits Aventis HQs and requests all audit records related to Study3014. Aventis provides all blacked-out documents.	Ross Timeline	
Thu 03/06/2003			At a closed meeting between DAIDP and AIDAC, the Division tells the advisory committee about DSI's findings and its concerns about the integrity of Study3014's data.	AIDAC Meeting 3-A, 12/14/06, FDA Brief and Transcript pg 123-4	
Sun 06/01/2003		✓	OCI's SA West determines that of 220 patients interviewed from Kirkman-Campbell's site, 201 did not participate in the trial and	OCI 04-NEL-707-00 40 Files	

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**	**	**	another 57 questionnaires were marketed "return to sender". Only fifteen of 220 patients said they participated.	**	**
Wed 06/18/2003		✓	Kirkman-Campbell is arrested and arraigned.	OCI 04-NEL-707-00 40 JAF	
Thu 07/03/2003	✓		Aventis provides 77-page "proposed response" to Question 1.A.1 in the FDA's 7/24/03 Approvable Letter. The proposed response is written into a pre-meeting briefing package in advance of planned 7/24/03 meeting with the CDER Anti-Infective Division.	Disk "NDA 21144 Letter Date 7/3/03."	
Thu 07/24/2003	✓		DSI Inspects clinical site of Jeffrey McLeod in Virginia; finds he has submitted falsified data and issues a NIDPOE on 8/24/05.	NIDPOE Ltr, DSI File	FU w/ this PI's data
Sun 08/24/2003	✓	✓	DSI issues NIDPOE letter to Dr. Jeffrey McLeod in Virginia for submitting falsified data to Study3014.	NIDPOE Ltr, DSI File	
Fri 08/29/2003		✓	Kirkman-Campbell indicted.	OCI 04-NEL-707-00 40 JAF	
09/??/2003	✓	✓	DSI conducts 8 additional inspections; refers three PIs to OCI.	Ross Timeline	FU w/ these PI's data
09/??/2003	✓		Medical Team Leader's memo for resubmission is entered into DFS; Division Director requests last paragraph be "softened."	Ross Timeline	
10/??/2003	✓	✓	Aventis meets with FDA and brings 17 infectious disease consultants who had been briefed on the outcome of Study3014, but not on the data integrity issues.	Ross Timeline	
Fri 10/17/2003	✓		Aventis submits Completed Response to FDA's 1/24/03 approvable letter.	Approval Hx in PDF Files	
Thu 10/23/2003		✓	Kirkman-Campbell pleads guilty to one count of Mail Fraud in relation to Study3014.	OCI 04-NEL-707-00 40 JAF	

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11/??/2003	✓		Medical Team Leader revises his memo and places it into DFS.	Ross Timeline	
Mon 12/01/2003			DATE APPROXIMATE Aventis notifies FDA that Dr. Pierce has committed fraud in conducting study 4017 and was also a PI in Study3014.	OCI Case File 04-CHI-707-0148	
Wed 01/07/2004			OCI opens a criminal case against Dr. Keith Pierce in Detroit, MI	OCI Case File 04-CHI-707-0148	
02/??/2004	✓		FDA Division Director signs off on TL memo for 2nd cycle	Ross Timeline	
03/??/2004	✓		Original TL memo for 2nd cycle entered into DFS	Ross Timeline	
Wed 03/24/2004		✓	Kirkman-Campbell is sentenced to 57 months for committing fraud in connection with Study3014. The Court also orders her to pay over \$900,000 in restitution and \$557,000 in criminal fines. She begins serving her sentence immediately.	OCI 04-NEL-707-0040 JAF	
Thu 03/25/2004	✓	✓	DSI issues a consult concluding that "the integrity of the data from all sites involved in Study3014 cannot be assured with any degree or confidence." DSI Specifically states data from Sites 1129, 759, 1892, 965 and 1057 should be excluded.	Ketek Timeline (C) from CDER; DSI Consult in Ekey Electronic File	
Thu 04/01/2004	✓		FDA approves Ketek, without reference to risk of hepatotoxicity relative to benefit.	Ross Timeline	
Thu 05/13/2004			OCI's SA West opens a case on Achreja; case closes 3/6/07 after AUSA finds no prosecutorial merit.	CIR, 04-NST-707-0410	
Fri 08/20/2004			Sanofi acquires Aventis S.A.	EIR 5/25/06	
Wed 10/27/2004			EIR undertaken at Sanofi Aventis focusing on adverse event reporting. Few discrepancies are found, and the EIR is classified as NAI.	EIR 5/25/06	
Fri 12/31/2004			The individual companies of Sanofi and Aventis merge on	EIR 5/25/06	

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**	**	**	this date, forming Sanofi Aventis US, LLC, which becomes a single legal entity, chartered in Delaware.	**	**
05/??/2005			Three cases of severe liver injury reported by NC Medical Center, resulting in one death and one patient's placement on the liver transfer list.	Ross Timeline	
05/??/2005	✓		Aventis files Medwatch report with minimal information regarding patient(s) at Carolinas Medical Center	Ross Timeline	
07/??/2005			DATE APPROXIMATE TO SUMMER 2005. Aventis visits NC Medical Center and obtains additional information regarding the three liver injuries, but does not provide additional details to Medwatch.	Ross Timeline	
Fri 01/20/2006			FDA learns the Journal Annals of Internal Medicine is going to publish an article describing three cases of liver failure secondary to Ketek use; puts up information on FDA website.	CDER Timeline (C)	
02/??/2006	✓		Aventis submits its perspective on hepatic risk profile of Ketek, but does not include the pathology data it collected from from NC Medical Center the previous summer.	Ross Timeline	
Thu 03/02/2006		✓	Kirkman-Campbell tells OCI's Bob West that Aventis' study manager (Grethe) knew she falsified data	Original CIR, 7-T-709-0263	
Thu 03/09/2006			OCI's Ekey opens investigation of Aventis	Original CIR, 7-T-709-0263	
Tue 03/21/2006			Literature: Study published in the Annals of Internal Medicine recommend judicious use of Ketek following three acute liver failures in patients at Carolinas Medical Center in Charlotte, NC.	Literature File	
Thu 05/25/2006	✓		EIR undertaken at Sanofi Aventis focusing on adverse event reporting. The EIR is classified as NAI.	EIR 5/25/06	

Ketek Fact Chronology

5/2/2007 12:36 PM

Date & Time	Reg TL	3014 TL	Fact Text	Source(s)	Unresolved
Thu 06/08/2006			SA Ekey interviews Kirkman-Campbell in prison. She says both Aventis and PPD employees knew of the problems at her study site, including blood sample splitting. She admitted telling a senior PPD monitor that she made up charts and mixed blood samples. Before an FDA inspection, Grethe, Khosla, Mike (LNU) and an Aventis MD came to her site and cleaned her paperwork, giving her a stack of forms to sign. She said she tried to get out of the trial by Grethe threatened her with a lawsuit and jail if she left.	Kirkman-Campbell MOI	
Mon 06/12/2006			SA Ekey interviewed Robert McCormick, PPD's VP of QA. McCormick stated he could not discuss specifics of 3/4/02 teleconference with Aventis because of confidentiality agreement.	McCormick 6/12/06 MOI, P. 1	
Thu 07/06/2006			SA Ekey interviews Beth Mills (nee: Heding), who was a CRA for PPD. She conducted several of the audits at Kirkman-Campbell's site, at least two with Aventis employees present. Was there when Aventis cleaned up Kirkman-Campbell's files before an FDA inspection. She showed evidence of clinical trial fraud to Grethe and Khosla, but they minimized it or ignored it.	Mills MOI	
Thu 07/06/2006			SA Ekey interviewed John Reynolds, who described how he found evidence of sample duplication and abnormal randomization in Kirkman-Campbell's data. Although present on the 3/5/02 teleconference with Aventis, he recalled little of it. Identified "Master Treat" file as PPD's repository of all e-mail relating to Study3014.	Reynolds 7/6/02 MOI	
Tue 09/12/2006			SA Ekey re-interviewed Robert	McCormick	

Ketek Fact Chronology

5/2/2007 12:36 PM

Date & Time	Reg TL	3014 TL	Fact Text	Source(s)	Unresolved
**	**	**	McCormick. McCormick said he recommended to Tropmann that Aventis exclude Kirkman-Campbell's data and he believed Tropmann passed that recommendation on to Aventis.	9/13/06 MOI, P. 2	**
Fri 12/01/2006			SA Ekey interviewed Cathy Tropmann, PPD Director, who said she was the study director over Study3014 but was not present for the teleconference with Aventis on 3/5/02. She said Aventis conducted some analysis on the Kirkman-Campbell data, but it was not supplied to PPD.	Tropmann MOI	
Fri 12/01/2006			Ekey interviews Tropmann	Tropmann MOI	
Fri 02/09/2007	✓		Aventis submits an sNDA with a black box warning regarding myasthenia gravis patients and updating several sections of Ketek's labeling.	Label Approval History in pdf.	
Mon 02/12/2007	✓		FDA approves a black-box warning for Ketek making myasthenia gravis a contraindication and updating several sections of the drug's labeling. The new label is placed on the Internet immediately.	Label Approval History in pdf.	
Mon 02/26/2007			OCI Task Force Case reassigned to SA Loveland.	Original CIR, 7-T-709-0263	

