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Jesper Grarup, CHIP,
Dept. of Infectious Diseases &
Rheumatology, Rigshospitalet,
Copenhagen, Denmark
Tel: +45 35 45 57 57
Jesper.grarup@regionh.dk

Acceptance Rate of Clinical Study Endpoints and Adequacy of Source Documentation: Experience from the Clinical Study Endpoint Review in NEAT001/ANRS143

F Wit[1*], PO Jansson[2], C Schwimmer[3], EC George[4], M Estée Török[5], J Berenguer[6], JD Kowalska[7], C Wallet[3], J Saillard[8], A Diallo[9], AL Pozniak[10], F Raffi[11], J Grarup[2], and NEAT001/ANRS143 Study Group

[1]Amsterdam Institute for Global Health and Development, Department of Global Health, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands; [2]CHIP, Department of Infectious Diseases and Rheumatology, Section 2100, Rigshospitalet – University of Copenhagen; [3]INSERM U897, Bordeaux, France; [4]MRC Clinical Trials Unit at UCL, London, UK; [5]University of Cambridge, Department of Medicine, Cambridge, UK; [6]Hospital General Universitario Gregorio Marañon, Madrid, Spain; [7]Wojewodzki Szpital Zakazny, Warszawa, Poland; [8]Service de Recherches cliniques et Thérapeutiques VIH/sida, ANRS, Paris, France; [9]Service de Vigilance des Recherches Cliniques, ANRS, Paris, France; [10]Chelsea and Westminster Hospital, NHS Foundation Trust, London, UK; [11]University Hospital, Nantes, France

BACKGROUND

NEAT001/ANRS143 was an open-label, randomised, non-inferiority study comparing raltegravir + darunavir/r (RGV+DRV/r) vs. tenofovir/emtricitabine + darunavir/r (TDF/FTC +DRV/r) in HIV-infected antiretroviral naïve adults. Primary efficacy outcome was a compo-site of virological and clinical events by week 96.

MATERIALS AND METHODS

The Endpoint Review Committee (ERC) reviewed the following types of event: AIDS defining events, serious non-AIDS defining events, grade 4 adverse clinical events, grade 2 to 4 rashes, deaths, and immune reconstitution syndrome events. Clinical trial units collected and translated supporting documen-tation (SD) related to the investigator reported events. A coordinator checked events and SD for consistency and completeness. The Endpoint Review Committee (ERC) determined if clinical events met predefined diagnostic criteria in categories 'confirmed' or 'probable'. The ERC of 12 experienced, independent clinicians served in groups of 3 conducting individual reviews in writing, blinded to treatment arm and other reviewers' assessment. Differences of opinion were adjudicated in a second review round by direct dialogue between reviewers. 'Confirmed' events required adequate supporting documentation such as laboratory, radiographic or pathology diagnostic reports. 'Probable' events were typically based on clinical criteria alone. For rash events, possible drug relationship was evaluated.

RESULTS

Of the 164 serious and 3964 adverse events reported in the study, 133 events qualified for endpoint review, for a total of 153 adjudications of which 46% were agreed among reviewers in a second round review, see table 1 for clinical study endpoints and table 2 for rash events.

Sixty of 111 per protocol endpoints were confirmed (n=53) or probable (n=7), which equals an acceptance rate of 54%. In two confirmed cases, supporting documentation was partly adequate and evaluation uncertain.

Of 51 rejected events, 13 had insufficient supporting documentation, 2 were recurrent events. The difference in rejection rate between treatments was not significant with 41% rejected events in the RGV+DRV/r arm compared to 52% in the TDF/FTC +DRV/r arm, see table 3. Of the 42 rash events 30 were evaluated probably or possibly related to the study drug.

The IRIS acceptance rate was low (3/18), demonstrating the difference in perception of IRIS in the daily clinical patient management compared to the stricter protocol definition of IRIS.

CONCLUSIONS

Blinded endpoint review prevented unacceptably high false positive event rates. Our experience shows that real time ascertainment of clinical endpoints is crucial for appropriateness of the overall results. Rejected events jeopardize the statistical power in this and probably all clinical trial designs. The rejection rate was not indicative of poor study conduct on the contrary overreporting prevented missing events, which would have adversely impacted the trial. The vast majority of accepted events were confirmed and with adequate source documentation. This reflect investigators general awareness of the importance of adequate supporting documentation and the possible differences between event criteria in daily pragmatic clinical management and event criteria as defined in the protocol.

Table 1

Review result for clinical study endpoints

	All	AIDS	Serious non-AIDS	IRIS	Clinical Grade 4 AE	Death
Total reviewed events	111	24	35	18	29	5
Per Protocol Endpoints (confirmed + probable)	60	11	18	3	23	5
Confirmed Events	53	11	16	2	19	5
SD* adequate	42	10	11	1	16	4
SD* sufficiently/only partly adequate	10/1	1/0	5/0	0/1	3/0	1/0
Probable Events	7	0	2	1	4	0
SD* sufficiently/ only partly adequate	6/1	0/0	2/0	0/1	4/0	0/0
Rejected Events	51	13	17	15	6	0
not fulfil criteria, SD* adequate	17	3	9	2	3	0
not fulfil criteria, SD* sufficiently adequate	21	8	3	8	2	0
not fulfil criteria, SD* only partly adequate	13	2	5	5	1	0

* Supporting documentation

Table 2

Review results for rash events

	Rashes
Total reviewed events	42
Confirmed Events (grade 2-4)	28
SD* adequate	6
SD* sufficiently/only partly adequate	19/3
Rejected Events (grade 1 or not a rash)	14
not fulfil criteria, SD* adequate	4
not fulfil criteria, SD* sufficiently adequate	5
not fulfil criteria, SD* only partly adequate	5

* Supporting documentation

Table 3

Review result by treatment arm

	AIDS		Serious non-AIDS		IRIS		Clinical Gr. 4 AE		Death	
	A	B	A	B	A	B	A	B	A	B
Total reviewed events	14	10	18	17	8	10	19	10	4	1
Per Protocol Endpoints (conf. + probable)	6	5	11	7	2	1	14	9	4	1
Confirmed Events	6	5	9	7	2	0	12	7	4	1
SD* adequate	6	4	7	4	1	0	11	5	3	1
SD* sufficiently adequate	0	1	2	3	0	0	1	2	1	0
SD* only partly adequate	0	0	0	0	1	0	0	0	0	0
Probable Events	0	0	2	0	0	1	2	2	0	0
SD* sufficiently adequate	0	0	2	0	0	0	2	2	0	0
SD* only partly adequate	0	0	0	0	0	1	0	0	0	0
Rejected Events	8	5	7	10	6	9	5	1	0	0
not fulfil criteria, SD* adequate	3	0	5	4	2	0	2	1	0	0
not fulfil criteria, SD* sufficiently Adequate	5	3	1	2	4	4	2	0	0	0
not fulfil criteria, SD* only partly adequate	0	2	1	4	0	5	1	0	0	0

A: RGV +DRV/r; B: TDF/FTC +DRV/r; *Supporting documentation

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Jansson, Karoline Jensen, Zillah Maria Joensen, Ellen Moseholm Larsen, Christiane Pahl, Mary Pearson, Birgit Riis Nielsen, Stentoft Reilev, Ilse Christ, Desiree Lathouwers, Corry Manting, Remko Van Leeuwen, Alpha Diallo, Bienvenu Yves Mendy, Annie Metro, Juliette Saillard, Sandrine Couffin-Cadiergues, Anne-Laure Knellwolf, Lucia Palmisano, Esther Aznar, Cristina Barea, Manuel Cotarelo, Herminia Esteban, Iciar Girbau, Beatriz Moyano, Miriam Ramirez, Carmen Saiz, Isabel Sanchez, Maria Yllescas, Andrea Binelli, Valentina Colasanti, Maurizio Massella, Olga Anagnostou, Vicky Gioukari, Giota Touloumi. ***Study Investigators:*** Brigitte Schmied, Armin Rieger, Norbert Vetter, Stephane De Wit, Eric Florence, Linos Vandekerckhove, Jan Gerstoft, Lars Mathiesen, Christine Katlama, André Cabie, Antoine Cheret, Michel Dupon, Jade Ghosn, Pierre-Marie Girard, Cécile Goujard, Yves Lévy, Jean-Michel Molina, Philippe Morlat, Didier Neau, Martine Obadia, Philippe Perre, Lionel Piroth, Jacques Reynes, Pierre Tattevin, Francois Raffi, Jean Marie Ragnaud, Laurence Weiss, Yazdan Yazdanpanah, Patrick Yeni, David Zucman, Georg Behrens, Stefan Esser, Gerd Fätkenheuer, Christian Hoffmann, Heiko Jessen, Jürgen Rockstroh, Reinhold Schmidt, Christoph Stephan, Stefan Unger, Angelos Hatzakis, George L Daikos, Antonios Papadopoulos, Athamasios Skoutelis, Denes Banhegyi, Paddy Mallon, Fiona Mulcahy, Andrea Antinori, Massimo Andreoni,,Stefano Bonora, Francesco Castelli, Antonella D'Arminio Monforte, Massimo Galli, Adriano Lazzarin, Francesco Mazzotta, Vincenzo Vullo, Jan Prins, Clemens Richter, Dominique Verhagen, Van Eeden, Andrzej Horban, Manuela Doroana, Francisco Antunes, Fernando Maltez, Rui Sarmento-Castro, Juan Gonzalez Garcia , José López Aldeguer, Bonaventura Clotet, Pere Domingo, Jose M Gatell, Hernando Knobel, Manuel Marquez, Martin Pilar Miralles, Joaquin Portilla, Vicente Soriano, Maria-Jesus Tellez, Anders Thalme, Anders Blaxhult, Magnus Gisslen, Alan Winston, Julie Fox, Mark Gompels, Elbushra Herieka, Margaret Johnson, Clifford Leen, Anton Pozniak, Alastair Teague, Ian Williams. ***Endpoint Review Committee***: Mark Alastair Boyd, Jesper Grarup, Per O Jansson, Nina Friis Møller, Ellen Frøsig,Moseholm Larsen, Philippe Morlat, Lionel Piroth, Vincent Le Moing, Ferdinand W N M Wit, Justyna Kowalska, Juan Berenguer, Santiago Moreno, Nicolas J Mu¤ller, Estée Török, Frank Post and Brian Angus. ***Sub-study working groups:*** Deenan Pillay, Charles Boucher, Vincent Calvez, Simon Collins, David Dunn, Zoe Fox, Carlo Federico Perno, Marta Boffito, Adriana Ammassari, Andrea Antinori, Wolgang Stoehr, Brigitte Autran, Reinhold Ernst Schmidt, Michal Odermarsky, Colette Smith, Rodolphe Thiébaut, Jose Arribas, Jose Ignacio Bernardino De La Serna, Antonella Castagna, Stephane De Wit, Xavier Franquet, Hans-Jackob Furrer, Christine Katlama, Amanda Mocroft, Peter Reiss, Raffaella Bucciardini, Nikos Dedes, Vincenzo Fragola, Elizabeth C George, Marco Lauriola, Rita Murri, Pythia Nieuwkerk, Bruno Spire, Alain Volny-Anne, Brian West, Hélène Amieva, Andrea Antinori, Josep Maria Llibre Codina, Laura Richert, Wolgang Stoehr, Alan Winston

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