THE REJECTION OF THE STUDY "BAY 11.643"[*].

Critical analyses of the methodological and ethical shortcomings of the protocol

Ethics Committee (CHE, Comité Hospitalario de Ética) and Institutional Review Board (CIREI, Consejo Institucional de Revisión de Estudios de investigación), Hospital Privado de Comunidad of Mar del Plata City, Buenos Aires Province, Argentina[**]

January 30, 2012

On September 16, 2010, the Institutional Review Board (CIREI) of the Hospital Privado de Comunidad (HPC) of Mar del Plata City, Buenos Aires Province, Argentina, notified the Central [Research] Ethics Committee of Buenos Aires Province (CEC, Comité de Ética Central) of its decision to reject the study protocol "Bay 11643", because no reply from the sponsor on the objections made by the CIREI had been

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(*) Official title: "*A Randomized, Double-blind, Multicenter Trial to Evaluate the Safety and Efficacy of Sequential (Intravenous, Oral) Moxifloxacin Versus Comparator in Pediatric Subjects With Complicated Intra-abdominal Infection".* Description available at http://www.clinicaltrials.gov/ct2/show/NCT01069900 (Accessed January, 2012)

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received till then to the notes sent to Bayer Laboratories on May 5 and August 23, 2010.

In order to inquire about other qualified opinions about the issue, the CIREI contacted also with other IRBs, some of them belonging to centers listed as participants in Argentina, asking for their points of view on the shortcomings detected. Similarly, on June 21, 2011, a note was sent to the National Administration of Drugs, Food and Medical Technology (ANMAT, Administración Nacional de Medicamentos, Alimentos y Tecnología médica), Argentina's regulatory agency under the Ministry of Health of the Nation, communicating the process carried out and requesting information about whether the protocol continued under way in other centers in the country, if it had been modified in line with the objections raised, and so on.

The protocol with which the CIREI worked was the version 1.0 in Spanish language Bay 12-8039/11643, dated on Sept. 23, 2009. It was accompanied by the following documents, all of them in Spanish: 1) "Informed consent form and information for pediatric patients to parents or legal guardians of children 12 to 17 years old", specific version 1.0 for Argentina, dated on Dec. 14, 2009, based on the final master version 2.0, dated on Nov. 19, 2009; 2) "Patient acceptance form for the pediatric study in children 12 to 17 years old", specific version 1.0 for Argentina, dated on Dec. 4, 2009, based on the final master version 1.0, dated on Oct. 30, 2009, and 3) "Security information Appendix for the informed consent form and information for pediatric subjects for parents or guardians of children 12 to 17 years of age", specific version 1.0 for Argentina, dated on Dec. 14, 2009, based on the final master version 2.0, dated on Nov. 19, 2009.

It should be understood that any reference to the protocol made in this document refers specifically to the above versions.

The main point made in our observations was that the methodological design of the study did not consider the use of formal statistics tests to compare the results of the group treated with the study drug with those of the control group. This would impede evaluating the compared safety and efficacy (at levels of superiority, equivalence or non-inferiority), which are the study's primary and secondary objectives, respectively.

A further review of the protocol led us to conclude that its design was not only methodologically flawed but also lacked a strong ethical justification that would make its implementation essential. These conclusions are discussed below.

In spite of the commented rejection [last note about the issue, as mentioned above, dated June 21, 2011, to the ANMAT], on October 4, 2011 the study appeared as "terminated" at the Hospital Privado de Comunidad, in the online registry of clinical trials of the U.S. National Institutes of Health –NIH- (www.clinicaltrials.gov). According to the glossary provided on that web page, "terminated" means that the process of

recruiting or enrolling participants was halted prematurely and will not resume. However, as pointed out above, the study was never started in the HPC because it had been rejected. To our knowledge, in a similar situation would be other institutions elsewhere, for which the study is shown as terminated on *www.clinicaltrials.gov*, when in fact they never initiated it.

We want to stress here that the category "rejected", which would correspond to our case, is not in that glossary (NIH. Available at http://www.clinicaltrials.gov/ct2/info/#/Recruitment glossary -accessed January 2012-). We consider it necessary to incorporate this category, including the reasons for such rejection, in order to improve the transparency of the research process and to prevent possible misunderstandings

The lack of operational responses at all levels to our concerns and objections, and the mistake published on the website of the NIH, were the reasons that led us to make public this document

BACKGROUND

In 2003, it was stated that: “Fluoroquinolones are an important group of antibiotics widely used in adult patients because of their excellent tissue penetration and their bactericidal activity. They are not authorized for pediatric use (except for pseudomonas infections in cystic fibrosis), however, because of the potential for joint toxicity reported from studies in young animals. Despite the absence of official approval, fluoroquinolones are widely used in pediatrics as second-line antibiotics when all other treatments have failed. Most of the information available about pediatric use concerns ciprofloxacin, which is used in children much more often than the other members of this class. The published pediatric series have shown that the frequency of articular side-effects varies according to age: all the surveys have reported frequencies of around 0-1% in adults and 2-3% in children. Out of cystic fibrosis and severe infections in which no other treatment is possible, the only pediatric situations in which the fluoroquinolones are superior to standard treatments for children, in terms of the speed of recovery and comfort as well as the efficacy, are typhoid fever, severe *Shigella* dysentery, and severe enterobacterial meningitis”[1].

In 2006, the Committee on Infectious Diseases of the American Academy of Pediatrics (AAP) recalled that the indications for which fluoroquinolones are licensed by the US Food and Drug Administration (FDA) for use in children are complicated urinary tract infections, pyelonephritis, and postexposure treatment for inhalation anthrax, in view of its potential for arthrotoxicity, as it has been seen in the commented animal studies, and the reported association with reversible musculoskeletal events in both children and adults. They also recommended that fluoroquinolone use must be restricted to situations in which there is no safe and effective alternative to treat an infection caused by multidrug-resistant bacteria or to provide oral therapy when parenteral therapy is not feasible and no other effective oral agent is available[2] .

As pointed out above, the uncertainty regarding its safety arises from findings in studies with young animals in which fluoroquinolones were shown to cause irreversible injury to weight-bearing cartilage[3,4,5,6].

A non-randomized, controlled (against other antibiotics) cohort study involving children and adolescents younger than 18 years of age reported a 9.3-fold increased risk (95% CI; 1.20-195; P .02) of musculoskeletal adverse events associated with this group of drugs (in this case, the study focused on ciprofloxacin, ofloxacin and pefloxacin), with complete remission of the adverse event once the drug was withdrawn. The study, however, did not evaluate the long-term risks of these complications[7].

A meta-analysis which examined the use of fluoroquinolones in children younger than 18 years of age could not show major acute musculoskeletal adverse events, and found insufficient long-term data. The most relevant studies included in this meta-analysis focused on ciprofloxacin, oxafloxacin, levofloxacin and pefloxacin[8]. The authors of this review concluded that most studies lead to the conclusion that there is no clear association between musculoskeletal alterations and fluoroquinolone administration. They emphasized that even though such association could not be found, these drugs should not be used indiscriminately. However, when they are indicated, their therapeutic benefits should be given priority over those potential adverse events which are not supported by evidence.

Prolonged QT interval of the electrocardiogram is another adverse event currently under inquiry. Prolongation of the QT interval may result in tachyarrhythmias such as life-threatening *torsades de pointes*. All fluoroquinolones have the potential to induce prolongation of QT interval. Sparfloxacin was identified as having the greatest risk of inducing such prolongation, and was consequently withdrawn from the U.S. market. Moxifloxacin was reported to cause this effect occasionally[9].

The AAP recommendations[2] emphasized also an increase in fluoroquinolone resistance, pointing out that “despite the fact that the only indications for which a fluoroquinolone (ie, ciprofloxacin) has been licensed by the FDA for use in patients younger than 18 years are complicated urinary tract infections, pyelonephritis, and postexposure treatment for inhalation anthrax, there were approximately 520 000 prescriptions for fluoroquinolones written in the United States for patients younger than 18 years in 2002. Approximately 13.800 of those prescriptions were written for infants and children 2 to 6 years of age, and 2.750 were written for infants younger than 2 years”.[…]“One study in adult patients demonstrated that the proportion of susceptible *P aeruginosa* isolates decreased from 100% to 45% after 14 days of treatment”[…]”Studies from many countries have reported resistance to fluoroquinolones among *C jejuni*, *Shigella* species, *Salmonella* species, and shiga toxin-producing E. coli*”*. Increased fluoroquinolone resistance has also been reported

in *S pneumoniae* isolates: “There is evidence that resistance to fluoroquinolones is essentially a class effect. Thus, increased use of fluoroquinolones can be anticipated to result in an increase in strains of *S pneumoniae* that are resistant to all fluoroquinolones. Resistance of *P aeruginosa*, *P mirabilis*, *E coli*, and other common hospital pathogens has increased consistently as fluoroquinolone use has increased”. The recommendations concluded about this issue that that “the inappropriate use of fluoroquinolones in children and adults is likely to be associated with increased bacterial resistance to these agents”.

The AAP further expressed that “The use of a fluoroquinolone in a child or adolescent may be justified in special circumstances after careful assessment of the risks and benefits for the individual patient. Although there is no compelling evidence supporting the occurrence of sustained injury to joints in humans by a fluoroquinolone, the possibility that it occurs infrequently has not been excluded”.

Circumstances in which fluoroquinolones may be useful for the AAP include “those in which (1) infection is caused by multidrug-resistant pathogens for which there is no safe and effective alternative and (2) parenteral therapy is not feasible and no other effective oral agent is available”.

According to the AAP, appropriate uses should be limited to the following:

- exposure to aerosolized *Bacillus anthracis* to decrease the incidence or progression of disease (FDA licensed) (evidence grade III);
- urinary tract infections caused by *P aeruginosa* or other multidrug-resistant, Gram-negative bacteria (FDA licensed for complicated *E coli* urinary tract infections and pyelonephritis attributable to *E coli* in patients 1–17 years of age) (evidence grade II-2);
- chronic suppurative otitis media or malignant otitis externa caused by *P aeruginosa* (evidence grade II-3);
- chronic or acute osteomyelitis or osteochondritis caused by *P aeruginosa* (not for prophylaxis of nail puncture wounds to the foot) (evidence grade III);
- exacerbation of pulmonary disease in patients with CF” [cystic fibrosis] “who have colonization with *P aeruginosa* and can be treated in an ambulatory setting (evidence grade II-2);
- mycobacterial infections caused by isolates known to be susceptible to fluoroquinolones (evidence grade III);
- Gram-negative bacterial infections in immunocompromised hosts in which oral therapy is desired or resistance to alternative agents is present (evidence grade II-1);
- gastrointestinal tract infection caused by multidrug-resistant *Shigella* species*, Salmonella* species*, Vibrio cholerae,* or *C jejuni* (evidence grade II-2);

- documented bacterial septicemia or meningitis attributable to organisms with in vitro resistance to approved agents or in immunocompromised infants and children in whom parenteral therapy with other appropriate antimicrobial agents has failed (evidence grade III); and
- serious infections attributable to fluoroquinolone-susceptible pathogen(s) in children with life-threatening allergy to alternative agents

In short, the AAP does not recommend and in fact discourages fluoroquinolone use when other treatments are available, for safety reasons and mainly because of the risk of inducing increased bacterial resistance[2].

The Argentinean Health Technology Assessment Division of the Health Research Committee (Comisión Nacional Salud Investiga), under the Ministry of Health, carried out a systematic review on the musculoskeletal adverse events caused by fluoroquinolone use in pediatric patients[10], some of whose conclusions we have already quoted, which was later summarized and published[8]. The review states the following: "It is concluded that the incidence of tendon or joint adverse events (TJD) derived from fluoroquinolone use is low and inconsistent. Thus, the use of these agents should not be avoided when they are the only therapeutic option available. However, given their broad spectrum, fluoroquinolones should be avoided when there are other treatment alternatives, in order to minimize the likelihood of developing bacterial resistance, particularly of respiratory pathogens such as *S pneumoniae*. Fluoroquinolones are safe and effective antibiotics for the treatment of conditions for which they are specifically indicated. A presumed risk of arthropathy should not be an impediment in cases in which indication is appropriate". Even though the conclusion states that "this review does not support restrictions to fluoroquinolone use based on the risk of potential osteoarticular adverse events", it should be considered whether this conclusion applies to all the agents of this class or only to those included in the review (i.e., ciprofloxacin –the most extensively studied agent–, oxofloxacin, levofloxacin, pefloxacin and nalixidic acid).

METHODOLOGICAL SHORTCOMINGS

We want to stress first that it is astonishing for us that the study Bay 11643 is under way, having been introduced itself as one of safety and efficacy, when there are no completed study of the pharmacokinetics of the drug in children.

In fact, the same sponsor is currently conducting a study of this type. The purpose of that study is to describe the pharmacokinetics of moxifloxacin in children to establish the most appropriate dose for pediatric patients in the future, as well as to examine the safety of moxifloxacin in children with infections. The sponsor declares that the study results will be used to guide the dosage strategy in future clinical trials involving children[11].

Moreover, “Bay 11643” is presented as a“[…]*randomized, double-blind, multicenter trial to evaluate the safety and efficacy of sequential (intravenous, oral) moxifloxacin versus comparator*[…]. The comparative nature of the study is also mentioned in the information provided to parents. Nevertheless, the protocol later states that “*all efficacy analysis will be merely descriptive and no formal statistical tests will be performed”*. Therefore, this clinical trial is peculiar by being introduced as a comparative study asserting at the same time that the two treatment arms will not be compared.

IS THERE A BIOETHICAL JUSTIFICATION FOR A SAFETY STUDY OF MOXIFLOXACIN BASED ON THIS DESIGN?

The primary objective of the study “Bay 11643” is to determine the safety and efficacy of sequential (intravenous, oral) moxifloxacin versus intravenous ertapenem followed by oral amoxicillin/clavulanate in children and adolescents younger than 18 years.

The safety profile of moxifloxacin in animals is comparable to those of other fluoroquinolones[12].

No studies have been conducted in children to help establish whether the drug is safe, and the limited data on adverse events from studies involving other fluoroquinolones are not necessarily applicable to moxifloxacin. Therefore, the drug safety related to arthrotoxicity is uncertain. For instance, reports show a higher frequency of arthrotoxicity in children treated with pefloxacin compared to other fluoroquinolones[6], with a reported case of sequelae due to destructive polyarthropathy following long-term treatment (three months) with pefloxacin[13]. In fact, the eventual potential for arthrotoxicity induced by moxifloxacin (as well as QT interval prolongation) is what has motivated this investigation.

Furthermore, as we have commented, another study is currently being conducted by the same sponsor, with the declaimed purpose of describing the pharmacokinetics of moxifloxacin in children. The sponsor asserts that the study results will be used to guide the dosage strategy in future clinical trials involving children[11]. In view of what has been mentioned above, it is not clear for us why the sponsor is simultaneously conducting the study we are concerned with (BAY 11643). This procedure implies unreasonably superimposing phases in the research process.

If AAP recommendations are to be followed, from a bioethical point of view this kind of study can only be justified when there is no first-line treatment for this condition, when there is evidence of relative inefficacy or severe adverse events, or when the administration of parenteral drugs is not feasible. In that case, the study design should be one of relevantly superior efficacy (as its primary objective) and safety, or one of non-inferior efficacy but relevantly superior safety.

Additionally, the use of a new antibiotic agent as moxifloxacin in a population which does not require it, may facilitate the emergence of bacterial resistance, thus restricting its indication in populations with conditions which are currently treated with that agent. As noted, this is what is currently happening with fluoroquinolones as a drug class[2,8,10].

If the only purpose is to evaluate the drug safety (short and long-term arthrotoxicity and the consequences of QT interval prolongation), cohort studies involving all the cases in which a fluoroquinolone (in this particular case, moxifloxacin) is indicated as first-line treatment would be more than enough and ethically justified.

In conclusion, we do not find ethical grounds to justify a study as “Bay 11643”, exposing children and adolescents to an uncertain risk (even if this risk is likely to be low) with no readily apparent benefits, and potentially causing social harm if fluoroquinolone use is extended to conditions which have other treatment alternatives, since they may increase bacterial resistance to this group of useful drugs.

OBJECTIONS TO THE INFORMED CONSENT

In the informed consent, parents are told that intravenous and oral moxifloxacin is safe and well tolerated in adult patients for the approved indications and that a good level of tolerance is expected in children suffering from the condition mentioned in the study. This is “expected”, but there is no certainty, and that is the reason why the study is being conducted.

Parents are neither informed about the well-known findings in studies with young animals, nor the AAP recommendations. Instead, they are informed that a separate document called “Safety Information Appendix to the pediatric informed consent form for parents and legal guardians of 12 to 17-year-old children” will be provided to them at their request, but reading of this document is not considered essential, and it does not include the abovementioned information either.

BIOETHICAL DISCUSSION AND CONCLUSIONS

Among the different theories which could be applied in bioethical decision-making, we have considered relevant to the bioethical analysis of this case the so-called “Theory of Principles” developed by Beauchamp and Childress[14], and the precautionary principle.

The theory of Beauchamp and Childress describes four *prima facie* bioethical principles, i.e., they should always be respected, the only exception being a conflict with a higher moral duty.

These are: the principle of nonmaleficence (one ought not to inflict evil or harm), the principle of beneficence (one ought to do and promote good), the principle of autonomy (one should respect people's capacity to choose for themselves), and the principle of justice (distributive justice, understood as the equitable allocation of burdens and benefits within the members of a given social group).

The authors do not establish a hierarchical order with respect to these principles. If possible, the four principles should be respected, and if, on evaluating a given case, a conflict arises between any of the principles, it should be solved considering the consequences of prioritizing one over the other.

The Spanish bioethicist Diego Gracia Guillén, however, proposes hierarchical levels for these four principles[15]. He separates them into two levels of two principles each. The first (upper) level includes the principles of nonmaleficence and justice, representing common good. The second (lower) level includes the principles of beneficence and respect for autonomy, representing individual good.

The principles included in the first pair (nonmaleficence and justice) are indivisible. These duties –to benefit the social group–, Diego Gracia explains, arise from public consensus. For that reason, their grounds and scope are contained in the governing laws, and compliance with them is guaranteed by the binding force of law. In other words, individuals are bound by them even against their will.

The principles of beneficence and autonomy, in turn, are grouped together since, according to the current trends in the field of international law, human rights and bioethics, there is no possible beneficence if individual autonomy is not respected. What is desired to be emphasized is that, based on the principle of autonomy, it is the individual who decides what is best for him/her.

The first level focuses on the duty to respect basic rules of social coexistence, while the second level makes emphasis on the respect for the diversity of life projects.

For this particular case, we would like to point out that because of its design the study exposes vulnerable individuals (children) to an uncertain harm with no expectations of prospective benefits.

In addition, conducting a study on a vulnerable population, with uncertain risks and no apparent benefits, and which is moreover capable to facilitate the spread of bacterial resistance to fluoroquinolones, goes also against the principle of justice.

Since the study participants are underage children, surrogate consent must be obtained. We have already explained the study flaws concerning the informed consent and consider that, regarding this, the study violates additionally the principle of autonomy.

Furthermore, apart from the theory of Beauchamp and Childress, this type of study would also be violating the precautionary principle, which states that if an action has a suspected risk of causing harm, one should refrain from taking that action[16].

To conclude, in view of all that has been explained in this analysis, we believe that the study is unacceptable from a bioethical point of view.

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