Designing and interpreting the results of first-time-to-man studies

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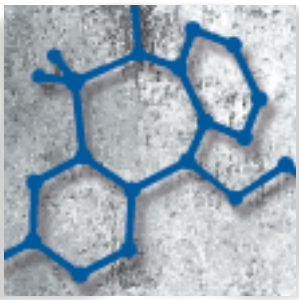

First human administration of a new chemical entity (NCE) constitutes a critical step in drug development. The primary objective of such a study is the assessment of the short-term safety and tolerability of single and multiple doses of the NCE in healthy volunteers. Secondary objectives are to obtain preliminary data on the pharmacokinetics and pharmacodynamics using surrogate or biomarkers of the beneficial as well as the adverse effects of the drug. Interpretation of safety data should be cautious and mainly based on comparisons with placebo. A special focus should be made on the assessment of adverse events, liver enzymes, and cardiac repolarization. Well-designed, first-time-to-man studies should determine the safety of the NCE in humans and predict the dose range that may be used to safely and accurately conduct further clinical trials in the target patient population based on safety data (maximum tolerated dose), pharmacodynamics (minimum active dose, duration of action, and dosage regimen), and pharmacokinetics (dosage regimen).

Keywords: *first-time-to-man study; phase 1 trial; drug development; adverse events; liver toxicity; cardiac repolarization; QT interval prolongation*

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The path of a new drug from concept to medication may be divided into two phases, namely drug discovery and drug development. Clinical pharmacology, also known as phase 1 or human pharmacology, constitutes one of the most critical steps in drug development, as it forms the link between drug discovery and preclinical and clinical drug development, and produces the necessary basis for the confirmatory phase 2 and 3 clinical trials of a new chemical entity (NCE) in patients with the target indication. Clinical pharmacology constitutes an exploratory stage of drug development during which essential information should be provided about the safety, the pharmacokinetics (quantitative description of the disposition of a drug in the body or a body compartment over time: "what does the body do to the drug?"), and the pharmacodynamics (quantitative description of drug effects, activity, or toxicity: "what does the drug do to the body?").

Clinical pharmacology starts with the first-time-to-man (FTTM) administration of an NCE and lasts throughout drug development. Assessment of the short-term safety and tolerability of single and multiple doses of an NCE in healthy volunteers, whatever the route of administration, is the main objective of the FTTM studies. In addition, preliminary pharmacokinetics and pharmacodynamics (ie, surrogate or biomarkers of expected pharmacological activity and/or unwanted side effects) should be secondary objectives of these studies.

Study design

No specific guidelines exist; only three gold standards apply: the study should be double-blind and placebo-controlled, and safety is paramount. One dose level may be evaluated in small subgroups of 3 to 5 subjects (2 to 3 subgroups per dose level) and the dose must be increased only after careful review of all the data available from the previous dose level. Indeed, "go/no go" decisions about further drug development must be made at all stages of the FTTM studies. These decisions

Selected abbreviations and acronyms

AE	*adverse event*
ALT	*alanine aminotransferase*
AP	*alkaline phosphatase*
AST	*aspartate aminotransferase*
EMEA	*European Agency for the Evaluation of Medicinal Products*
FTTM	*first-time-to-man*
NCE	*new chemical entity*
VAS	*visual analogue scale*

determine the progression of the studies, firstly to the next higher dose, then from the single- to the multiple-dose study, and finally from one population (healthy subjects) to another ("at-risk" population or patient population). The aim is to define the maximum tolerated dose (MTD) in humans based on the evaluation of adverse events (AEs), routine laboratory tests, vital signs (temperature, respiratory rate, supine and standing blood pressure, and heart rate), and electrocardiograms (ECG).[1-3] A sequential parallel-group or a crossover design may be used for single-dose studies. Multiple-dose studies are done using a sequential parallel-group design with a duration of administration of 1 to 4 weeks, usually 2 weeks. Eight to 12 subjects are usually included per dose level (6 to 9 subjects on active treatment versus 2 to 3 subjects on placebo).

Both designs have pros and cons. The main advantages of a sequential design are that a larger number of subjects are exposed to the NCE and that naive subjects are exposed at each dose level, and thus there are no concerns about a possible carryover effect in pharmacokinetics and/or pharmacodynamics. No wash-out is required, reducing the time factor. Modifying dose levels or dosing occasions according to the results obtained at lower doses is easy and allows flexibility; it has optimal feasibility and no problems with drop outs. The disadvantages of the sequential design are that there is no placebo control for individual variations in the various parameters assessed and that there is no measure of within-subject variability and dose proportionality in pharmacokinetic parameters. The main advantage of crossover studies is that they have a better design for assessing any dose–effect relationship; there is a placebo control for individual variations and an enhanced statistical power. However, there are many disadvantages: a smaller number of subjects are exposed; each subject is exposed more than once with the possibility of a carryover effect (especially due to the limited knowledge available about the compound at this stage of the development); and finally replacement of possible drop-out subjects can turn into a nightmare, prolonging the duration of the study and/or leading to a loss of the increased statistical power if, for any reason, subjects are not replaced.

Adverse events

The most usual ways of monitoring AEs include spontaneous reporting by the subject and the investigator's own observations. Occasionally, a symptom checklist may be used; however this sometimes leads to an overestimation of the number of AEs.

In the field of central nervous system (CNS) drugs, it is also possible to assess subjective effects on mood and alertness by self-rating using either visual analogue scales (VASs) or questionnaires. The two most frequently used VASs are the Leeds Analogue Rating Scales (LARS) and the Bond and Lader VAS.[4,5] The LARS consists of eleven 10-cm long VASs on which subjects compare their present feelings with their usual status. Average scores for the three sedation scales, "tiredness," "drowsiness," and "alertness," are used to measure perceived sedation. The Bond and Lader VAS consists of sixteen 10-cm bipolar analogue scales with two opposite mood-related adjectives at the end of the scales. It refers to the subjects' present feelings without any reference to their usual status. Factorial analysis of these scales yields three factors, alertness, contentedness, and calmness.[5]

Sleep may also be assessed using VASs. The most frequently used scale is the Leeds Sleep Evaluation Questionnaire (LSEQ).[6,7] It consists of ten 10-cm long scales. It is completed by the subject about 30 minutes after awakening and is used to rate subjective impressions of the ease of getting to sleep, the quality of sleep, the awakening from sleep, and behavior following waking (early morning hangover).

Among the various questionnaires used to assess mood and behavior, the Profile Of Mood Scale (POMS) and Addiction Research Center Inventory (ARCI) are frequently used. The POMS[8] is a 65-adjective checklist. Subjects rate each item on a 5-point scale from 0 ("not at all") to 4 ("extremely"), and 7 scores are obtained: anger/hostility, confusion/bewilderment, depression/dejection,

fatigue, friendliness, tension/anxiety, and vigor. The ARCI[9,10] consists of 49 true or false questions from which were derived five major scores: the morphine–benzedrine group (a measure of euphoria), the pentobarbital–chlorpromazine–alcohol group (a measure of sedation), the lysergic acid diethylamide (LSD) group (a measure of dysphoria), and the benzedrine group and the amphetamine-sensitive scales for stimulant effect.

Other specific scales or questionnaires may be used depending on the drug evaluated and the dimension of action being investigated: the Spielberger State/Trait Anxiety Inventory[11] for anxiety; various questionnaires to assess abuse liability of drugs[10-12]; the Clinical Institute Withdrawal Assessment-Benzodiazepine (CIWA-B)[13] to assess and monitor benzodiazepine-like withdrawal; or the Simpson-Angus and Barnes Akathisia scales to assess the extrapyramidal side effects of neuroleptics. VASs may also be used to assess nausea, pain, thirst, etc.

AE reporting is one of the most difficult tasks in clinical trials. The interpretation may vary among investigators. Training and clear explanations should be provided, especially for AE coding, in order to standardize as much as possible. As already mentioned, double-blind, placebo-controlled conditions are mandatory. Indeed, placebo may produce adverse events with an overall incidence ranging from 7.4%[14] (24 studies conducted in the same Clinical Pharmacology Unit in Europe and involving 430 subjects) to 19%[15] (109 studies outsourced to various Clinical Pharmacology Units in Europe and involving 1228 subjects). The most frequently encountered AE after placebo administration are headache (2% to 7%) and drowsiness/asthenia (10%). This "nocebo" effect emphasizes the need for placebo-controlled studies.

Liver tests

Hepatotoxicity is the leading reason for removal of an NCE from the market or for discontinuation of drug development. A recent study of agents approved and subsequently banned because of safety concerns showed that in 28% of cases (8 cases in this study), liver damage was either the only reason (4 cases) or one of the reasons (4 cases) for discontinuation.[16] Of 130 drugs withdrawn from the market for safety reasons between 1964 and 1992, adverse effects on the liver were responsible in 18% of cases.[17] Drug development of 29 out of 320 NCEs was terminated due to clinical toxicity, including 9 cases (31%) due to effects on the liver.[18] Information from preclinical studies using cultured hepatocytes, covalent binding in microsomes, etc, predicted possible liver effects in some cases.

These data illustrate both the importance of detecting a potential hepatotoxic effect of an NCE and the possibility of false-negative results during preclinical and clinical tests on hepatotoxicity. One of the key objectives of phase 1 trials is to assess the safety of an NCE in humans, and in particular to document the absence of hepatotoxicity.

True liver tests are albumin, serum prothrombin time, and/or partial thromboplastin time, but these are not sensitive enough to detect early liver damage. Usual screening for liver damage in clinical trials comprises total bilirubin (TB), alanine aminotransferase (ALT or serum glutamate pyruvate transaminase [SGPT]), aspartate aminotransferase (AST or serum glutamate oxaloacetate transaminase [SGOT]), and alkaline phosphatase (AP). Lactate dehydrogenase (LDH) is too insensitive and too nonspecific, and gamma-glutamyltransferase (gamma-GT) is too nonspecific for monitoring liver damage. Increases in AP and gamma-GT may be induced by drugs. Both are indicators of cholestasis and are nonspecific.

It is also important to clearly define drug-induced liver disorders.[19,20] Unless a liver biopsy has been performed, the lesions should not be named according to the histological findings, eg, cirrhosis, chronic liver disease, hepatic necrosis, or hepatitis. The preferred term is liver injury. The term liver injury should be used if there is an increase of over 2N (N representing the upper limit of the normal range) in ALT or conjugated bilirubin or a combined increase in AST, AP, and TB, provided one of them is above 2N. No other biochemical test is specific to liver disorder. Increases in ALT, AST, AP, or TB between N and 2N indicate abnormality of liver tests, not liver injury. Isolated increases in AST, AP, or TB even above 2N should be considered as a simple biochemical abnormality and not necessarily a sign of liver injury.

There are three types of liver injury: hepatocellular liver injury, characterized by an increase in ALT alone of over 2N or R>5 (R=ALT/AP, each measured as a multiple of N); cholestatic liver injury, characterized by an increase in AP alone of over 2N or R<2; and mixed liver injury, characterized by an increase in both ALT (over 2N) and AP, and 2<R<5. An acute liver injury corresponds to an increase in liver test values over less than 3 months. In contrast, a chronic liver injury is an increase in liver test

values over more than 3 months. Severe liver injury refers to the presence of, in order of increasing severity, jaundice, prothrombin level below 50%, and hepatic encephalopathy.

ALT is the most sensitive and the most specific routine laboratory test available to detect early liver damage. Thus, any elevation of ALT above the upper limit of the laboratory should be considered and any significant increase in ALT during the early phase, most notably in repeated-dose studies in healthy volunteers, may lead to discontinuation of development of a drug. The value of 2N is often considered as a threshold to define a potentially clinically significant abnormality (PCSA). However, ALT elevation to levels above the upper limit of normal range (ULN) has been observed in healthy young subjects treated only with placebo with a prevalence ranging from 12% to 22% in the literature *(Table I)*.[21-23] This prevalence increases after placebo treatment lasting more than 1 week. In a recent review of data gathered from 152 hospitalized healthy young male volunteers participating in randomized, double-blind, placebo-controlled, 14-day, ascending-multiple-dose safety studies, the prevalence of ALT levels above ULN was 18.4%, with 13% having an abnormality of liver tests (value between N and 2N) and 5% a liver injury (value above 2N). Infectious disease (mononucleosis, toxoplasmosis, or viral infection) may explain this elevation in a few subjects, but it generally remains unexplained. The usual causes of increases in ALT and AST, such as physical activity (30% to 40% increase in ALT and 30% to 70% increase in AST associated with an increase in creatine phosphokinase [CPK]), hypercaloric and hyperglucidic diet (100% increase in ALT and AST),[24,25] excessive consumption of alcohol (20% to 30% increase in ALT and AST), and overweight (10% to 60% increase in ALT and AST), can be ruled out. Indeed, overweight subjects are excluded from participating in such studies and the restrictions during the study (alcohol intake forbidden, standardized normal diet, and no strenuous physical activities) are easy to control as the subjects are hospitalized throughout the study.

The duration of hospitalization may have a major impact on the prevalence of transaminase elevation on placebo, since most cases occur during the second week of hospitalization. One factor may be an imbalance between reduced physical activity and maintained caloric intake. Kanamaru et al[26] reported ALT elevation in a group of subjects who rested for 7 days, contrasting with an absence of significant changes in a control group of subjects who engaged in daily physical exercise. However, other studies involving bed rest for a week or more (space medicine, metabolic studies) did not report ALT elevation.[27]

Author	Population	Number of studies	Duration of administration	Prevalence
Wyld et al*	49 males	6	4–16 days	12.2% (n=6)
Kobayashi et al[21]	104 males	-	1–7 days	12.5% (n=13)
Merz et al[22]	100 males (19–45 years)	13	7–31 days (mean 14 days)	22% (n=22)
Merz et al[22]	100 males (19–45 years)	13	7–31 days (mean 14 days)	22% (n=22)
Rosenzweig et al[23]	93 males (18–40 years)	13	14 days	20.4% (n=19)

French phase 1 club: increase in ALT levels after placebo (1996)**

Subjects exposed	Duration of administration	ALT<N	1N≤ALT≤1.5N	1.5N≤ALT≤2N	2N≤ALT≤3N	ALT>3N	Prevalence
78 males	7 days	75	1	2	0	0	3 (4.0%)
152 males (18–40 years)	14 days	124 (81.6%)	14 (9.2%)	6 (3.9%)	6 (3.9%)	2 (1.3%)	28 (18.4%)

N = upper limit of the normal range

Table I. ALT increase above upper limit of normal range in healthy subjects treated with placebo. * Unpublished communication, 1991; ** unpublished communication, 1996.

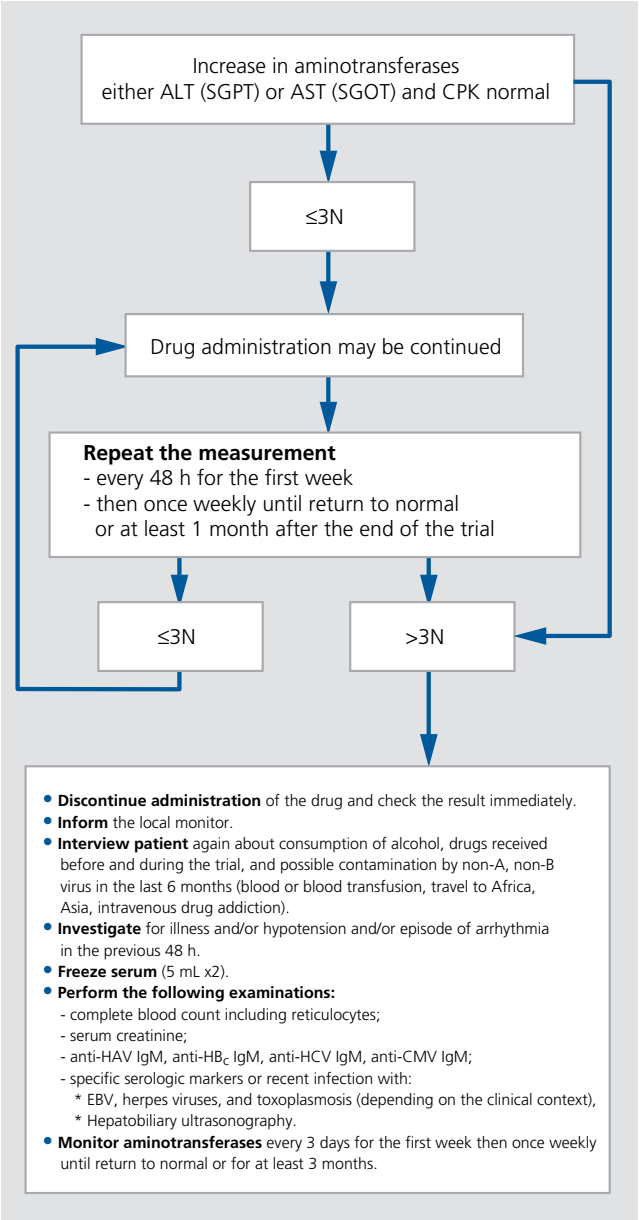

Figure 1. Increase in aminotransferase (expressed as a multiple of the upper limit of normal range [N] for the laboratory performing the assay).
ALT: alanine aminotransferase; SGPT: serum glutamate pyruvate transaminase; AST: aspartate aminotransferase; SGOT: serum glutamate oxaloacetate transaminase; CPK: creatine phosphokinase; HAV: hepatitis A virus; IgM: immunoglobulin; HB_c: hepatitis B core; HCV: hepatitis C virus; CMV: cytomegalovirus; EBV: Epstein-Barr virus.
Reproduced from reference 30: Benichou C. Management of adverse events during clinical trial. In: Benichou C, ed. *Adverse Drug Reaction. A Practical Guide to Diagnosis and Treatment.* Chichester, UK: John Wiley and Sons Ltd; 1994:223-232.

The composition of the diet may play a role. Porikos et al[24] showed that a combination of excess calories and a high sucrose intake was associated with enzyme elevation. The role of carbohydrates was further confirmed by an 8-day, three-way, crossover study in 12 healthy subjects comparing a high-fat diet (58% fat) providing 4500 kcal/day, a high-carbohydrate diet (32% sugar, 27% carbohydrates) providing 4400 kcal/day, and a "healthy" diet providing 1900 kcal/day. Whereas liver function tests remained normal in all the subjects on the healthy and high-fat diets, significant increases in ALT levels sometimes of more than 100% were observed in 5 of the 12 subjects on the high-carbohydrate diet. In most phase 1 trials, the diet provides less than 2500 kcal/day with a reasonable proportion of carbohydrates, but the carbohydrate intake was not always closely maintained within predefined limits.

The identification of clinically significant abnormalities of liver enzymes should be done on a case-by-case basis, taking into account an absolute threshold, usually the upper limit of the normal range (below this threshold, any value would be considered as a spontaneous variation), and a variation from baseline exceeding spontaneous variation (for instance, a 50% increase in the baseline value or an increase exceeding 20% of the upper limit of the normal range).[28,29] Decision charts to manage liver tests abnormalities have been determined following consensus meetings *(Figure 1)*[30] and are helpful to the investigator because they define when a drug should be discontinued (usually increase in ALT and/or AST above 3N with CPK normal) and the procedures to be followed to identify a possible cause other than the investigational drug. They are also useful to the sponsor as they standardize the procedure to be followed by the various investigators.

Cardiac repolarization

QT interval prolongation is a serious drug safety issue that should be properly addressed in drug development. Class III antiarrhythmic agents, such as amiodarone, sotalol, and bretylium, and class Ia antiarrhythmic agents, such as quinidine, procainamide, and disopyramide, are designed to intentionally prolong cardiac repolarization. However, a number of drugs have been shown to prolong cardiac repolarization unintentionally to such a degree that potentially life-threatening vesticular tachycardia called torsades de pointes may

result.[31] Several drugs are known to delay repolarization and to be associated with a prolongation of QT interval and possibly torsade de pointes: tricyclic antidepressants, antipsychotics (thioridazine, chlorpromazine), antihistamines (terfenadine, astemizole), antiinfectives (erythromycin, chloroquine, halofantrine), and miscellaneous drugs (cisapride, terodiline, furosemide, prednisolone, and beta-agonists).[32-34] Prolongation of cardiac repolarization is easily identified using ECG. Increased QT intervals in a patient are indicative of prolonged cardiac repolarization. However, because the QT interval is dependent on heart rate, it has to be corrected into a new variable independent of heart rate, called the corrected QT interval (QTc). Various equations have been proposed for this. The most widely used is Bazett's formula ($QTc = QT/\sqrt{RR}$). This formula gives an excellent correction for a heart rate value of 60 bpm. However, it overestimates (undercorrects) QTc at low heart rate and underestimates (overcorrects) QTc at high heart rate values.[35] Fridericia's formula ($QTc = QT/\sqrt[3]{RR}$) seems to have better predictive properties than Bazett's formula.[36-38]

In 1997, the European Agency for the Evaluation of Medicinal products (EMEA) proposed a "points to consider" document for the assessment of the potential for QT interval prolongation by a noncardiovascular medicinal product.[39] Several papers in the literature also emphasize the need to assess cardiac repolarization.[40,41] During phase 1, ECGs are collected from healthy, normal subjects, usually males, several times before, during, and after drug administration. The potential for QT interval prolongation of a noncardiovascular NCE should be assessed in a randomized, double-blind, placebo-controlled study, and with a sufficient number of doses to be able to characterize the dose–response relationship, including doses sufficiently higher than the proposed therapeutic dose to demonstrate a no-effect outcome. The time course of ECG effects should be evaluated according to the pharmacokinetic profile of the parent compound, as well as its active (toxic) metabolites if appropriate, after a single dose as well as at steady-state plasma concentrations. This timing should coincide with the expected C_{max} of the NCE or when the maximum concentration in the target cardiac cell is expected.

The EMEA document also emphasized that, at present, automatic readings from 12-lead ECGs are generally not considered sufficiently accurate and reliable. Holter may be useful to assess the occurrence of arrhythmia, but this is also inaccurate and not reliable enough for QTc readings, as it does not correlate sufficiently well with 12-lead ECG recorded at the same time. Therefore, manual reading of QT intervals by trained personnel is recommended.

Thus, according to the EMEA document, the QT interval should be measured using standard 12-lead recording (at 25 and 50 mm/s including a long lead II with at least 10 QRS complexes) with manual reading. The measurement of QT interval and QT dispersion should be assessed as the mean of 3 to 5 beats. In general, the U wave should not be included when the QT interval is measured. Both mean change from baseline and raw data should be adequately reported. Change in T-wave morphology and/or the occurrence of a U wave constitute important warning signs, which have the same significance as prolongation of QTc.

Automatic ECG reading indeed yields more conservative results than manual reading. QTc interval calculated according to Bazett's formula is on average 19 ms (range: -86 to +47 ms) shorter when measured manually than when measured automatically by a Marquette Mac 15 apparatus.[37] In a recent review of 866 ECGs recorded during a single-ascending-dose FTTM study, the manual reading (average of 3 beats measured in V_2) of QTc interval calculated using Bazett's formula was 16 ms shorter (range: -77 to 105 ms) and the QTc interval calculated using Fridericia's formula 23 ms shorter (range: -65 to +121 ms) than automatic measurement from a Marquette Mac 6 (Patat, unpublished data). Automatic QTc reading may therefore be thus sufficient for the monitoring of cardiac repolarization in real time in FTTM studies. However, the individual values vary widely from -90 to +100 ms and caution should be taken. However, automatic reading is particularly unreliable when there are difficulties in the measurement of the QT interval, such as in cases of a flat, broad, or notched T wave, in the presence of a U wave, when a P wave superimposes the T wave, or when the downslope of the T wave is distorted by noise. In such cases, QT should be checked by manual reading.

Holter recording is even less accurate and produces QTc values which may be over- or underestimated depending on the ECG lead assessed. The measurements of QTc from Holter were 24 ms shorter (range: -100 to 55 ms) in V_1 and 13 ms longer (range: -42 to

62 ms) in V_5 than QTc values from standard ECG when comparing the same complexes (Christiansen et al, presented at the 5th International Congress of Ambulatory Monitoring, 1992).

QTc is always 20 to 30 ms longer in females than in males, justifying different acceptable ranges (450 ms for males and 470 ms for females) *(Table II)*.

There is a diurnal variation of QTc interval. The QTc is longer (about 19±7 ms) during sleep than during waking hours when calculated at a heart rate of 60 bpm in 15 normal subjects. This may be due to increased vagal tone or sympathetic withdrawal.[46,47]

The QTc interval may be longer in some patient populations. QTc is longer in cardiac patients (mean QTc is 407 vs 417 ms in matched age and gender controls; QTc>440 ms in 25% [7 out of 28] of patients vs 3% [1 out of 28] of controls).[48] QTc is longer in cirrhotic patients (440 vs 394 ms in matched controls) and increases with Child-Pugh Score (QTc>440 ms in 50% of cirrhotic patients [44 out of 94 patients], 25%, 52%, and 63% patients for Child-Pugh A, B, and C, respectively, and 5% of controls [2 out of 37]).[49]

When examining data for individual patients, it is important to separate random, nonsystematic variability from variability caused by the drug. In order to be able to interpret any QTc change from baseline, it is mandatory to know the within-subject variability over the time of ECG. This may be studied by looking at QTc changes observed in placebo-treated subjects. Pratt et al[48] showed that 50% (14 out of 28) of healthy male subjects had at least 1 of the 40 ECGs recorded during the 6-day period of the study with a QTc value above a threshold of 440 ms. In the same study, 71% (20 out of 28) of cardiac patients had at least one QTc value above 440 ms when receiving placebo treatment.[48] The average QTc fluctuation or variability over 24 hours in normal men, measured as the difference between the shortest and the longest QTc value recorded, was 56±15 ms[48] or 59±12 ms.[50] Individual healthy male subjects (n=20) had a wide range of QTc fluctuations over 24 hours which averaged 76±19 ms (range: 35–108 ms) when QTc was measured by Holter recording.[51] Among these subjects, the QTc interval increased to over 440 ms in 11 of the 20 subjects (55%) during the 24-hour monitoring period. It even exceeded 500 ms in 1 of the 20 subjects.[51] When looking at the

	Males	Females	Both genders
Moss,[42] 1993			
Mean ± SD (ms)	410±10	420±20	
Range (ms)	380–440	370–480	
n	222	198	
Rassmussen et al,[43] 1991			
Mean all day (ms)	392	421	
Range (ms)	346–438	376–467	
n	30	30	
Gunput et al,[44] 1995			
Range (ms)			378–441
n	641	343	984
Patat et al, 1998*			
Mean ± SD (ms)	404±14		
Range (ms)	360–440		
n	280		
Adamson et al,[45] 1998			
Mean ± SD (ms)	389±20	405±21	
n	701	290	

Table II. QTc interval (Bazett's formula) of 12-lead ECG in healthy subjects. * Unpublished data, 1998.

fluctuations observed during the first 12 hours of dosing of healthy young subjects hospitalized in a clinical pharmacology unit, the mean fluctuation was 31 ms in 118 male and female subjects[52] and 31±14 ms (range: 4–63 ms) for 82 male subjects (Patat, unpublished data). Finally, the average maximum increase from baseline observed postdose in placebo-treated subjects was 17 ms over 8 hours postdose[52] and 14.0±12.7 ms over 12 hours postdose (Patat, unpublished data). Patients with cardiac disease show a greater spontaneous variation and a somewhat exaggerated QT response to drug effect.[48]

Based on these data in healthy subjects, it may be concluded that individual changes of QTc of less than 40 ms reflect normal biological and methodological variability and are unlikely to indicate drug effects, that individual changes between 40 and 60 ms are probably beyond normal biological and methodological variability and indicate possible proarrhythmogenic drug effects, and that individual changes above 60 ms exceed the normal biological and methodological variability, and indicate proarrhythmogenic drug effects.

Current guidelines place emphasis on two types of flags: raw QTc and delta values (change from baseline). There is little agreement among the scientific community on what constitutes a prolonged QTc interval. The Food and Drug Administration (FDA) in the United States has not issued any sort of formal guidance on the matter, but the EMEA has issued a guidance document.[39] The EMEA proposes that changes in QTc intervals between 30 and 60 ms are likely to represent a drug effect, and changes greater than 60 ms "raise clear concerns about the potential risk." Also, if the raw QTc interval is greater than 450 or 470 ms for males or females, respectively, then this too is evidence of prolonged QTc interval, even if only values above 500 ms "raise clear concerns about the potential risk." Morganroth et al[51] and Garson[53] recommend that a change in QTc interval greater than 75 ms or a maximal QTc interval of 500 ms is clinically abnormal. They consider the upper limit of normal as 440 ms. Using the observed placebo variability, Pratt et al[48] calculated that an increase in QTc interval >35 ms while receiving drug therapy is likely to represent a drug effect at the 95% confidence interval.

Finally, in addition to a prolongation of the QTc interval, a change in T-wave morphology and occurrence of a U wave constitute important warning signs of similar significance to a QTc prolongation.

When interpreting QTc values, various factors influencing QT interval prolongation should be taken into account: prolonged baseline QT interval (long QT syndrome), gender, bradycardia, cardiac or other diseases (myocardial ischemia, heart failure, stroke, or cirrhosis of the liver), and electrolyte disturbances (hypokalemia, hypomagnesemia, or hypocalcemia).

An additional QT parameter was proposed by the EMEA guidance, QT dispersion. QT dispersion (QTd) is increasingly thought to be of importance. QTd is defined as the difference between the shortest and the longest QT interval in a set of 6 to 12 ECG leads and, as such, describes the interlead QT variability. QTd reflects regional dispersion or inhomogeneity of ventricular repolarization. Since dispersion of ventricular repolarization is associated with enhanced vulnerability to ventricular arrhythmias, QTd was proposed as a simple predictor for the propensity of ventricular arrhythmia. Normal values range from 40 to 60 ms for a 12-lead ECG. Threshold values are individual increases in QTd of more than 100% and an absolute dispersion above 100 ms.[39] Measurement of QTd is the most controversial recommendation, as it is a new measure not readily available or in clinical use; its prognostic value in cardiac disease still needs to be established. Methodological issues still exist (number of leads to be used, correction for heart rate, correction for missing values) and there are large errors regardless of the method applied in QTd measurement: the coefficient of variation (CV) ranges from 20% (within-day) to 30% (between-day) compared with CV of 3% to 5% for QTc.

When studying an NCE with no preclinical findings indicating QT prolongation, ECG data should be generated in at least 100 subjects in early phase 1 and/or 2 studies, paying particular attention to the dose–effect relationship, steady state plasma levels, gender effect, age effect, and metabolic capacity (if a metabolite is involved). Drug–drug interactions with inhibitors or inducers of the NCE's metabolism also need to be considered to look for potential cardiac effects.

When studying an NCE with preclinical findings indicating QT prolongation, more extensive investigation is required. The early clinical testing should be performed in at least 200 subjects. If QTc prolongation or other ECG effects are observed in these early studies, it is recommended that ECG measurements be made in all patients included in the clinical development

program. ECG should be recorded prior to drug intake and at steady-state plasma levels of the drug and/or its metabolite, and plasma potassium levels should also be measured at the same time. Holter monitoring should be considered to determine whether QTc prolongation complicates into arrhythmia and/or T-wave morphological changes. Phase 2 and/or 3 studies must include the likely at-risk groups, eg, women, the elderly, patients of different phenotypes, and patients with concomitant disease, such as renal or hepatic impairment or cardiovascular disease with and without diuretic treatment. ❑

El diseño y la interpretación de los resultados de estudios realizados por primera vez en el ser humano.

La administración por primera vez en el ser humano de una nueva sustancia química (NSQ) constituye un paso crítico en el desarrollo de fármacos. El objetivo primario de un estudio de este tipo es la evaluación de la seguridad en el corto plazo y de la tolerancia a dosis únicas y múltiples de la NSQ en voluntarios sanos. Son objetivos secundarios el obtener datos preliminares de la farmacocinética y farmacodinámica utilizando sucedáneos o marcadores biológicos tanto para los efectos beneficiosos como para los efectos adversos de la sustancia. La interpretación de la seguridad de los datos debe ser cuidadosa y basarse principalmente en comparaciones con placebo. Debe prestarse especial atención a la evaluación de los efectos adversos, las enzimas hepáticas y la repolarización cardíaca. Los estudios realizados por primera vez en el hombre, bien diseñados, deben determinar la seguridad de la NSQ en seres humanos y predecir el rango de dosis en que puede ser empleada, para llevar a cabo futuros ensayos clínicos con seguridad y precisión en alguna población definida de pacientes, de acuerdo con datos confiables de dosis (dosis máxima tolerada), de farmacodinámica (dosis activa mínima, duración de la acción y régimen de dosificación) y de farmacocinética (régimen de dosificación). ***Conception et interprétation des résultats***

Conception et interpretation des résultats des études de première administration à l'homme

La première administration à l'homme d'une entité chimique nouvelle (ECN) représente une étape critique dans le développement d'une molécule. L'objectif principal d'une telle étude est d'évaluer la sécurité et la tolérance à court terme après administration de doses unique et multiples d'une ECN chez des volontaires sains. Les objectifs secondaires sont d'obtenir des données préliminaires pharmacocinétiques et pharmacodynamiques sur les effets tant bénéfiques qu'indésirables de la molécule en utilisant des substituts ou des marqueurs biologiques. L'interprétation des données de sécurité d'emploi doit être prudente et basée principalement sur des comparaisons avec le placebo. L'évaluation des effets indésirables, les enzymes hépatiques et la repolarisation cardiaque doivent faire l'objet d'un intérêt particulier. Des études de première administration chez l'homme bien conduites doivent déterminer la sécurité d'emploi d'une ECN chez l'homme et prévoir la fourchette de dose utilisable afin d'effectuer ultérieurement avec précision et sans risque chez une population cible des études cliniques basées sur la sécurité (dose maximale tolérée), la pharmacodynamique (dose minimale active, durée d'action, schéma posologique) et la pharmacocinétique (schéma posologique).

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