



Doc. No.: U07-0134

<b>Substance/ Product:</b>	Clobutinol hydrochloride (Silomat <sup>®</sup> )
<b>Title:</b>	Expert statement on the non-clinical and clinical evaluation of the potential for delayed ventricular repolarization (QT Interval Prolongation) by Clobutinol.
<b>Authors/Institute /Department:</b>	Boehringer Ingelheim GmbH, D-55216 Ingelheim, Binger Strasse 173
<b>Date:</b>	30.08.2007
<b>Page 1 of 12, exclusive Appendices</b>	
<b>Confidential</b> © 2007 <b>Boehringer Ingelheim</b> <b>Proprietary confidential information</b> This report is the property of <b>Boehringer Ingelheim International GmbH</b> and may not - in full or in part - be passed on, reproduced, published or otherwise used without prior written permission	

## TABLE OF CONTENT

1	BACKGROUND .....	4
2	INTRODUCTION.....	4
3	CLINICAL EXPERIENCE WITH CLOBUTINOL.....	5
4	NON-CLINICAL INVESTIGATION PROGRAMME .....	5
5	CLINICAL INVESTIGATION PROGRAMME .....	6
6	CONCLUSION .....	11
7	ABBREVIATIONS .....	12
8	REFERENCES.....	12

## APPENDIX

- Appendix 1 Mean RR interval change to baseline in ms versus ECG time points for dose group 1 and dose group 2 for active drug and placebo.
- Appendix 2 Mean QT interval change to baseline in ms versus ECG time points for dose group 1 and dose group 2 for active drug and placebo.
- Appendix 3 Mean QTcF interval change to baseline in ms versus ECG time points for dose group 1 and dose group 2 for active drug and placebo.
- Appendix 4 Placebo corrected mean QTcF interval change to baseline in ms versus ECG time points for dose group 1 and dose group 2.

## 1 BACKGROUND

The active pharmaceutical ingredient clobutinol, a centrally acting cough suppressant, is available as sugar-coated tablets, solution, liquid and ampoules. The first Marketing Authorisation for clobutinol (tradenames e.g. Silomat<sup>®</sup>, Lomizat<sup>®</sup>) was granted on 01-MAY-1961 and it is now marketed internationally in many countries throughout the world. Based on the long lasting clinical experience clobutinol is marketed in many countries also as an “over the counter” drug, which means that patients may purchase and take clobutinol without prescription and advice by a healthcare professional.

In 2004 a preclinical publication [1] suggested that clobutinol might have an arrhythmogenic potential based on a newly identified effect of clobutinol on hERG K<sup>+</sup> channels.

In consultation with the German Regulatory Authority (BfArM) this publication together with a confounded (hereditary Long QT Syndrome, cardiac malformations and concomitant medication) clinical report of Torsade de Pointes triggered a programme consisting of non-clinical and clinical studies to investigate a possible effect of clobutinol on cardiac ion currents and the peripheral ECG.

## 2 INTRODUCTION

### Drug induced QT- prolongation and Torsade de Pointes

“Torsades de Pointes” (TdP) is a potentially life-threatening ventricular tachyarrhythmia characterised by QRS complexes continuously changing in morphology around the isoelectric line. This ventricular tachyarrhythmia is usually self-terminating. Critically, however, TdP can subsequently degenerate into ventricular fibrillation in about 20% of cases [2] and cardiac arrest and sudden death may then be the outcome. The exact incidence of drug induced TdP in the general population is unknown. It is estimated that the overall mortality, when a TdP occurs, is in the order of 10% - 17% [3].

Many conditions, acquired as well as congenital, may prolong ventricular repolarisation, measured as a QT interval prolongation in the ECG [4]. QT interval prolongation per se is not necessarily harmful and has been associated with changes in autonomic tone. However, when QT-prolongation is excessive it can lead to a potentially fatal Torsade de Pointes (TdP). QT interval prolongation is thus a risk factor and surrogate marker for TdP [5], albeit an imperfect one.

Generally, QT is considered conspicuous when the length of the QTc interval is greater than 440 ms (men) and 460 ms (women), although arrhythmias are most often associated with values of 500 ms or more.

Repolarisation abnormalities which result in a QT-prolongation can be divided into two broad groups. Depending on the underlying conditions a primary or idiopathic (congenital) form and an acquired form are known.

With respect to the acquired form drug induced QT prolongation is most common, with antiarrhythmics being the group of drugs most commonly implicated. Risk factors are organic heart disease (e.g. ischaemic heart disease, dilated cardiomyopathy, myocarditis), metabolic abnormalities (e.g. electrolyte disturbance, e.g. hypokalaemia (by far the most common cause), hypocalcaemia, hypomagnesaemia) and female gender (with possible gender related differences in specific cardiac ion current densities) [4].

Although at present, the proarrhythmic potential of a given QT prolongation cannot be reliably predicted, it has been well recognised that a prolonged QT interval (irrespective whether congenital or acquired) on the surface ECG can be associated with a small, but increased risk of TdP and/or sudden death.

During recent years drug-induced TdP has gained increasing attention and respective investigations have been introduced into new drug development. At present a commonly suggested threshold for clinical and “regulatory awareness” is approximately at one case of TdP per approx. 100.000 -1.000.000 clinical exposures [6].

### 3 CLINICAL EXPERIENCE WITH CLOBUTINOL

#### Patient Exposure

As the first Marketing Authorisation for clobutinol was granted on 1<sup>st</sup> May 1961, the product is now on the market for over 46 years and currently is marketed in 59 countries. It is estimated that approx. **200 mio patients** have received clobutinol.

#### Clinical Experience

Until today (data lock 25-AUG-2007) a total of 2 cases with “Torsade de Pointes” resp. “QT-prolongation” were reported. Neither of these cases was fatal. In both cases a broad range of confounding factors covering the whole spectrum of known causes for QT-Prolongation and other risk factors (congenital Long-QT Syndrom increased sympathoadrenergic activity, hypokalaemia) have been reported [4].

Even assuming under-reporting of serious adverse reactions by a factor of 10 [7], clobutinol would still remain below the aforementioned clinical and regulatory alert threshold. The very low number of reports still suggests a risk which is extremely low.

This explains why the cumulative spontaneous reports until today have not indicated a clinically relevant proarrhythmic potential.

### 4 NON-CLINICAL INVESTIGATION PROGRAMME

A series of tests were performed to assess the potential for clobutinol to prolong myocardial repolarization [8-11]. Clobutinol was shown to block hERG-mediated potassium channels expressed in HEK293 cells with an IC<sub>50</sub> of 3.7 µM. Its main metabolite norclobutinol had an IC<sub>50</sub> of 8.0 µM in the same model. Clobutinol was also shown to prolong the myocardial action potential in papillary muscle taken from the guinea pig in vitro in concentrations of 1 µM and higher. Norclobutinol also prolonged the action potential but at the concentration of 10 µM. Clobutinol was then administered orally to Labrador dogs [12] instrumented for the telemetric collection of ECG and haemodynamic data. Clobutinol was, however, poorly tolerated in the dogs causing marked CNS effects (aggressive behaviour and vomiting) such that the highest dose that could be tested was 30 mg/kg. Even this dose was associated with CNS effects. The estimated C<sub>max</sub> after the oral administration of 30 mg/kg was 3.3 µM and caused only a trend (4%, not significant versus vehicle) for QT-prolongation.

Further studies were therefore conducted in the anaesthetized beagle dog [13] with intravenous administration to allow for higher drug exposure. In the anaesthetized dog, a concentration-dependent prolongation of the QT interval was seen with the highest concentration (18.8 µM) causing a 15% prolongation of the action potential. It should be noted, however, that after intravenous administration in the anaesthetized dog there were only low levels of norclobutinol, in contrast to what was observed in the conscious dog after oral administration.

Taken together these studies demonstrate that clobutinol (and, to a lesser extent norclobutinol) inhibits myocardial repolarization and that this can be attributed to the blockade of hERG channels. At plasma drug concentrations shown to affect hERG-mediated repolarising current (i.e. concentrations approaching the  $IC_{50}$ ), there is a prolongation of the action potential in isolated myocardial tissue as well as in vivo. The relatively limited binding of clobutinol to plasma proteins suggests that this is not a relevant factor in comparing the in vitro and in vivo models. Based on these studies one would predict a prolongation of the QT interval when plasma drug concentrations reach or exceed a level of approximately 1  $\mu$ M. These studies thus provide a preclinical basis for understanding a potential QT interval prolongation with the clinical use of clobutinol. Whether the QT-prolongation caused by clobutinol is proarrhythmic cannot be assessed with these studies.

## 5 CLINICAL INVESTIGATION PROGRAMME

After a scientific advice meeting with the German Authority (BfArM) a multiple rising dose study in healthy volunteers with doses exceeding the highest recommended therapeutic dose of 80 mg clobutinol t.i.d. was performed. The protocol included a pharmacokinetic analysis of clobutinol and norclobutinol and an intensified surface ECG (electrocardiogram) monitoring to assess possible effects on QT/QT<sub>c</sub> interval.

### Trial objectives – General Aim and Endpoints

The primary objective of the study was to investigate safety parameters with special emphasis on ECG, tolerability and pharmacokinetics of clobutinol in healthy male and female volunteers following oral administration of a 80 mg single dose and of repeated rising doses of t.i.d. 80 mg (= maximum recommended therapeutic dose), 160 mg, 240 mg and 320 mg over 7 days plus a final dose in the morning of day 8 (= over 8 days).

There was no primary endpoint in a statistical sense in this study. Instead, safety and tolerability were closely assessed in a descriptive way based on physical examination, vital signs (BP, PR), clinical laboratory tests (haematology, clinical chemistry and urinalysis), observed adverse events, assessment of tolerability by investigator and particularly based on a 12-lead ECG the QT interval as well as the heart rate corrected QT<sub>c</sub> were assessed. As secondary endpoints pharmacokinetic parameters were determined after the first single dose of 80 mg (single dose group), and at predetermined times throughout the multiple dose rising treatments in order to establish a PK profile.

### Trial Design – Trial Population

This multiple rising dose trial was randomised, double-blind and placebo controlled within dose groups. 48 healthy male and female volunteers were to be included with oral administration of 80 mg clobutinol single dose and repeated rising doses of t.i.d. 80 mg (= maximum recommended therapeutic dose), 160 mg, 240 mg and 320 mg over 8 days. Within each dose group eight volunteers were to receive the active drug and four were to receive placebo. One dose was to be tested within each group. The dose groups to be evaluated are as outlined in the table below.

Dose group	1	2	3	4
Single Dose	80	n.a.	n.a.	n.a.
Multiple dose Part:				
Strength of each dose (mg)	80	160	240	320
Daily dose (mg)	240	480	720	960
Total number of multiple doses	23	23	23	23
No. of volunteers	12	12	12	12
No. of volunteers receiving placebo	4	4	4	4
No. of volunteers receiving drug	8	8	8	8
Volunteer number	1-12	13-24	25-36	37-48

The different dose groups were to be investigated consecutively in ascending order of daily doses, maintaining a time interval of at least 5 days between successive groups (i.e. between the last dosing day of the preceding dose level and the first dosing day of the subsequent dose level). The decision to proceed to the next dose group was to be based upon the clinical safety and tolerability data of the preceding dose group.

Besides the usual criteria for a withdrawal of an individual volunteer from the trial (e.g. volunteer withdraws consent without the need to justify the decision or is not longer able to participate for medical reasons) the protocol defined individual subject stopping rules namely a mean QTc interval > 500 ms in triple ECGs recordings at any time point or a prolongation > 60 ms versus baseline QTc.

Concerning the overall criteria and rules for stopping the clinical trial the protocol included the following criteria and rules:

- New toxicological findings or serious adverse events invalidate the earlier positive benefit-risk assessment. More specifically, the trial will be terminated if more than 50 % of the subjects in one dose step show drug-related and clinically relevant adverse events of moderate or severe intensity, or if at least one drug-related serious adverse event occurs which is considered to be unacceptable.
- The sponsor decides to discontinue the study.

The study was prematurely discontinued because of an epileptic Grand Mal attack in a 44 years old female volunteer which was considered as a Serious Adverse Drug Reaction.

### **Preliminary trial results**

#### **Dose group 1 (volunteer 01-12):**

In the single part of this group a single dose of 80 mg (n=8) or placebo (n=4) and afterwards multiple doses of 80 mg (n=8) or placebo (n=4) t.i.d. for 8 days were administered. The total administered daily dose of clobutinol was with 240 mg equal to the maximum recommended daily dose = recommended therapeutic dose in the CCDS.

No clinically relevant changes in vital signs or safety laboratory parameters were observed in the 240 mg group by the investigator.

#### **Dose group 2 (volunteer 13-24):**

In this group multiple doses of 160 mg (n=8) or placebo (n=4) t.i.d. for 8 days were administered. The total administered daily dose of clobutinol in this group was with 480 mg the double of the maximum recommended daily dose = overdose.

One severe Adverse Event (unclear transient neurological finding in one female volunteer (No. 19) leading to individual discontinuation of study medication) occurred in this dose group. The volunteer fully recovered.

#### **Dose group 3 (volunteer 25-36):**

In this group it was planned to administer multiple doses of 720 mg (240 mg t.i.d.) daily for 8 days.

One volunteer (No. 29) in this dose group presented after the second dose of 240 mg clobutinol a QTc increase versus baseline of 61 ms. Dosing in this volunteer was discontinued. ECG and safety monitoring was continued.

One volunteer (No. 30) in dose group three withdrew consent on the second day and dosing was discontinued subsequently.

After the fifth dose (afternoon dose of day two) another volunteer (No. 36) experienced a Grand Mal seizure.

Following this Serious Adverse Drug Reaction (listed side effect of clobutinol) the dosing for this group as well as the study as such was discontinued for all remaining volunteers. Safety monitoring was continued.

With the study discontinued the sponsor decided to request an accelerated central unblinded ECG evaluation.

### Preliminary central laboratory ECG analysis of mean QTc prolongation

Triple 10 second ECGs strips were obtained at 11 time points for the investigation of single dose 80 mg (V2= visit 2, only for dose group 1 = 80 mg). For the investigation of multiple dosing, triple ECGs were obtained at baseline and at 24 time points after dosing during the eight days of dosing (V3 = visit 3), four of these on day 1 (D1), 12 on day 2 to 7, and 8 on day 8 (D8).

Figure 1 displays the mean RR interval change to baseline in ms versus ECG time points. An increase of the RR interval refers to a decrease in heart rate. The almost parallel changes of heart rate for both dose groups with the respective placebo group and the wide overlap of the confidence interval indicate no obvious effect on heart rate.

**Figure 1:**

Mean RR interval change to baseline in ms versus ECG time points for dose group 1 (above graph) and dose group 2 (lower graph) for active drug (red line) and placebo (black line). (Please refer also to Appendix 1)

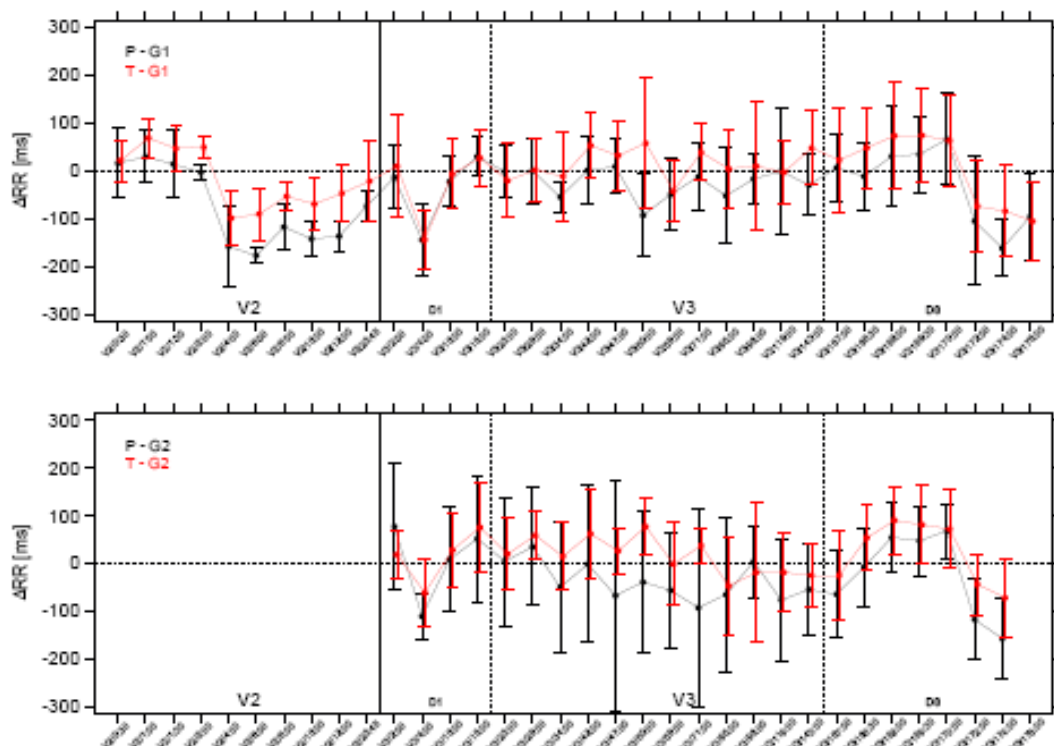


Figure 2 displays the mean uncorrected QT interval change to baseline in ms versus ECG time points. A dose dependent increase over time can be observed.

**Figure 2:**

Mean QT interval change to baseline in ms versus ECG time points for dose group 1 (above graph) and dose group 2 (lower graph) for active drug (red line) and placebo (black line). (Please refer also to Appendix 2)

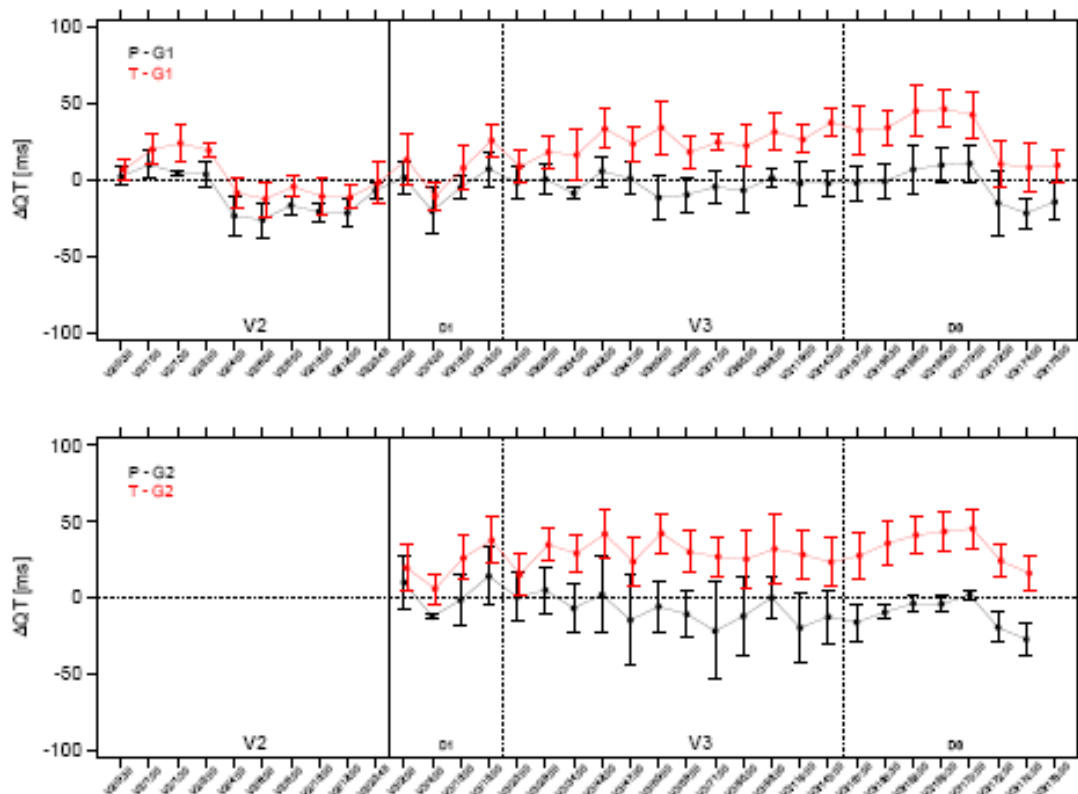


Figure 3 displays the mean heart rate corrected QTcF interval change to baseline in ms versus ECG time points. A dose dependent increase over time can be observed.

**Figure 3:**

Mean QTcF interval change to baseline in ms versus ECG time points for dose group 1 (above graph) and dose group 2 (lower graph) for active drug (red line) and placebo (black line). (Please refer also to Appendix 3)

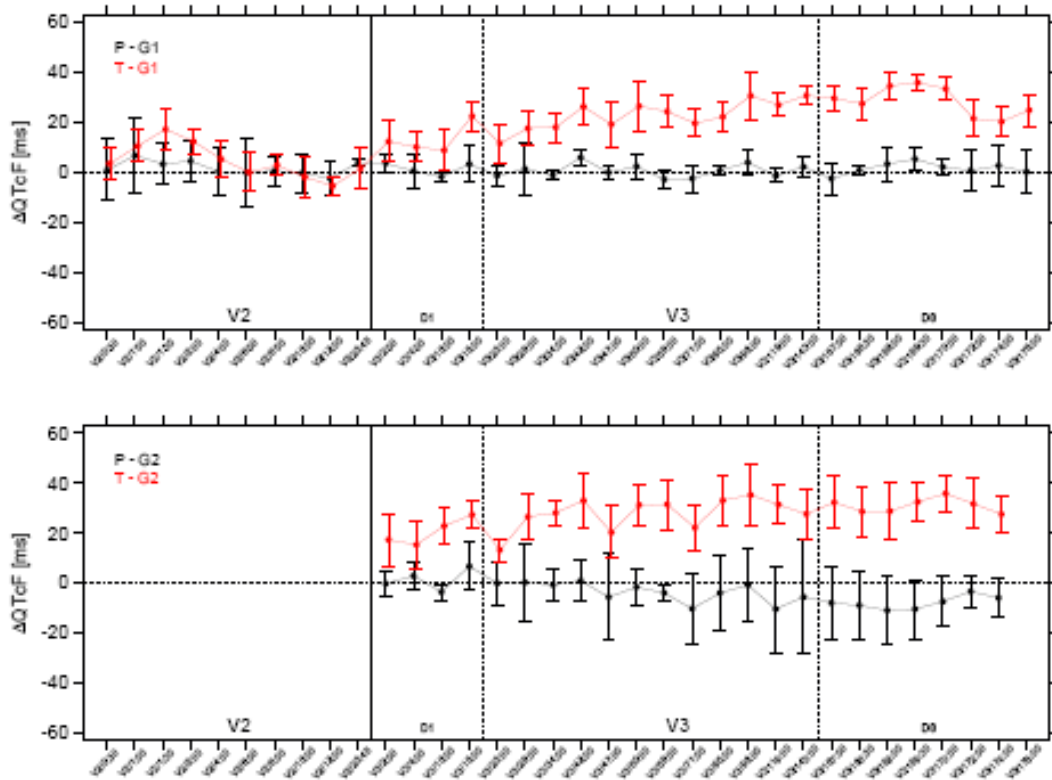
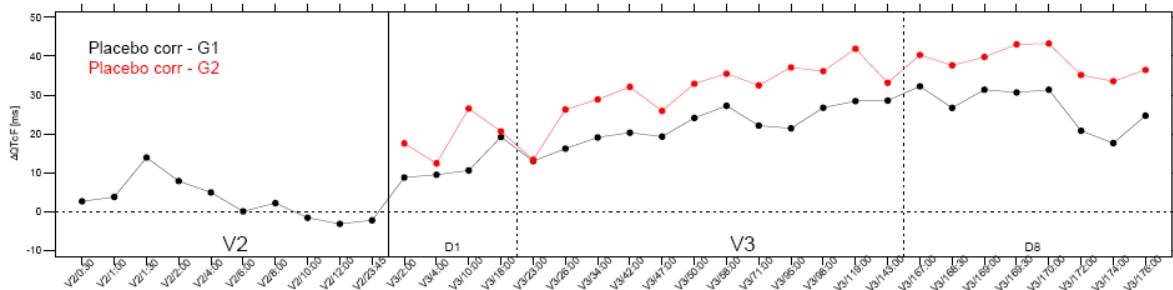


Figure 4 displays the placebo corrected mean QTcF interval change to baseline in ms versus ECG time points. A dose dependent increase over time can be observed.

**Figure 4:**

Placebo corrected mean QTcF interval change to baseline in ms versus ECG time points for dose group 1 (red line) and dose group 2 (black line). (Please refer also to Appendix 4)



As primary measure for QTc-prolongation, the placebo corrected maximum QTc change versus baseline on day 8 is suggested [7].

With this calculation method, the QTc increase is **32 ms for 240 mg clobutinol** daily (black line in Figure 4 above), and **43 ms for 480 mg clobutinol** daily (red line in Figure 4 above). For the third dose group (720 mg clobutinol daily), quality checked central ECG laboratory analysis is not yet available. However, the display of data based on automatic QT interval measurements indicates that the effects of the third dose group are higher than of the two lower dose groups for days 1 and 2 of treatment. As described above, the treatment was discontinued after day 2 in the third dose group.

Results on pharmacokinetics are not yet available to date

## 6 OVERALL CONCLUSION

Clobutinol has been developed long before drug induced TdP has been discussed or included into development considerations and has established its clinical safety and tolerability over many years of broad therapeutic use without any indication of cardiovascular risk observed. Therefore, the present findings are unexpected and new information.

The ECG results of the current clinical study in healthy subjects are consistent with the non-clinical study results and indicate that clobutinol has the potential to prolong the QTc interval. The observed changes are homogeneous, seem to be dose related and already for the maximum approved daily dose of concerning magnitude when compared to QTc prolongations seen with QTc prolonging reference drugs like moxifloxacin. Therefore, an arrhythmogenic potential of clobutinol must be assumed.

It has to be considered that clobutinol is indicated for a non life-threatening minor disease indication and in several countries is also available as “over the counter drug”, which means that patients may purchase and take the drug without prescription or further advice by a healthcare professional.

In light of the indication, the form of dispensing, the availability of potential alternatives, and the potentially life-threatening risk which may be associated with the observed QTc- prolongation, a positive benefit risk ratio for clobutinol both for OTC as well as for RX is no longer given.

In conclusion, Boehringer Ingelheim is taking measures to avoid or minimise any potential undue risk exposure for patients and in cooperation with competent health authorities intends to actively withdraw all its clobutinol containing products from the market.

## 7 ABBREVIATIONS

ADR	Adverse Drug Reaction
BI	Boehringer Ingelheim
BfArM	German Regulatory Authority
BP	Blood Pressure
C <sub>MAX</sub>	Maximum plasma concentration
CCDS	Company Core Data Sheet
ECG	Electrocardiogram
ETPC <sub>UNBOUND</sub>	Effective free therapeutic plasma concentration
HEK293	Human embryonic kidney cells 293
hERG	Human ether-a-go-go related gene (encoded voltage dependent potassium channel)
IC <sub>50</sub>	Concentration producing 50 % inhibition
I <sub>KR</sub>	Delayed rectifier potassium channel
LQTS	Long QT Syndrome (congenital form of QT-prolongation)
Main metabolite clobutinol	N-Demethylclobutinol, Nor-clobutinol
PO	Per os
PK	Pharmacokinetic
PR	Pulse Rate
QT-interval	Time between the onset of the Q-wave and the end of the T-wave of the ECG; a time incorporating ventricular depolarization and repolarization
QT- prolongation	QT prolongation is considered when the QTc interval is greater than 440 ms (men) and 460 ms (women), although arrhythmias are most often associated with values of 500 ms or more.
QT <sub>C</sub>	Heart rate corrected QT interval
TdP	Torsade de Pointes

## 8 REFERENCES

[1] P04-09151	Bellocq C, Wilders R, Schott JJ, Louerat-Oriou B, Boisseau P, Le Marec H, Escande D and Baro I A common antitussive drug, Clobutinol, Precipitates the Long QT2 Syndrome. <i>Molecular Pharmacology Fast Forward</i> 66, 1093-1102 (2004)
[2]	Salle P, Rey JL, Bernasconi P, Quiret JC, Lomhaert M Torsades de pointes. Apropos of 60 cases. <i>Ann Cardiol Angeiol (Paris)</i> 1985; 34: 381-8
[3]	Milon D, Daubert JC, Saint-Marc C, Gouffault J Torsade de pointes. Apropos of 54 cases. <i>Ann Fr Anesth Reanim</i> 1982; 1:513-20
[4] P06-07735	Viskin S, Justo D, Halkin A and Zeltser D Long-QT syndrome caused by non-cardiac Drugs. <i>Progress in Cardiovascular Diseases</i> , Vol. 45, No. 5, 2003: 415-427
[5]	Shah RR The significant of QT interval in drug development. <i>Br J Clin Pharmacol</i> 2002; 54:188-202
[6]	Malik M Detection of drug-induced proarrhythmia: Balancing preclinical and clinical studies <i>Heart Rhythm</i> , Vol 2, No 7, July 2005: 773-776
[7]	Wysowski DK, Bacsanyi J: Cisapride and fatal arrhythmia. <i>N Engl J Med</i> 1996; 335: 290-1
[8] U06-1456	Guth Brian Influence of clobutinol and its main metabolite (AF FB 256) on hERG-mediated potassium current in HEK293 cells and on action potential configuration in isolated guinea pig papillary muscle.
[9] U06-1118	Fuchs H In vitro plasma protein binding in dogs and humans
[10] U06-1090	Ludwig-Schwellinger E Clobutinol hydrochloride: In vitro inhibition studies on cytochrome P450 dependent metabolic reactions
[11] U06-1438	Ludwig-Schwellinger E, Bischoff Daniel Investigation of the in vitro metabolism of (14C)clobutinol hydrochloride and the human cytochrome P450 enzymes involved
[12] U06-1566	Markert M, Greischel A and Ganßer D Influence of Clobutinol (3,10 and 30 mg/kg PO) on hemodynamic and electrocardiographic parameters in conscious dogs
[13] U07-1537	Pragst I, Greischel A, Ganßer D Effects of clobutinol (1.0, 3.0 and 10.0 mg/kg IV) on systemic hemodynamics and the electrocardiogram in anesthetized dogs.