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OMICS Group has organized 500 conferences, workshops and national symposiums across the major cities including San Francisco, Las Vegas, San Antonio, Omaha, Orlando, Raleigh, Santa Clara, Chicago, Philadelphia, Baltimore, United Kingdom, Valencia, Dubai, Beijing, Hyderabad, Bengaluru and Mumbai.

People and ideas for innovation in healthcare

Spontaneous Ventricular Arrhythmias in Early Clinical Trials
A Report from a Single and Repeated Ascending Dose Study

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Background (1)

- Asymptomatic Ventricular Arrhythmias (VA) are reported in HV (up to 10%) and in patients without cardiac impairment (4 to 10%)
- Asymptomatic Ventricular Arrhythmias (VA) are reported infrequently in Phase 1 trials, so very few reliable data.
- The increased use of continuous ECG monitoring in this setting may lead to more frequent report on asymptomatic VA in Healthy Volunteers (HV)

a) *Evaluation of VA in early clinical pharmacology trials and potential consequences for later development.* A White Paper from the CSRC. Am Heart J 2010; 159: 716-29

b) *Premature ventricular complexes in the absence of identifiable heart disease.* JB Kostis, K McCrone, AE Moreyra, S Gotzoyannis, NM Aglitz, N Natarajan and PT Kuo; Circulation 1981, 63:1351-1356

Background (2)

- Occurrence of VA can raise question on go/no-go decision during a development program
- Decision has to be cautiously discussed in the context of lack of reliable data about the spontaneous occurrence of VA in HV
- And consequently no Guidelines or Recommendation on a consistent approach on how to decide

What Can be a «background» VA in a Phase 1 Clinical trial

- Asymptomatic
- Monomorphic premature ventricular complexes (PVCs) observed at baseline (and with the same rate after dosing)
- Non sustained monomorphic ventricular tachycardia(NSVT) (> 3 beats < 30 seconds) observed at baseline (and with the same rate after dosing)
- NSVT with a morphology suggesting a right ventricular outflow tract origin (RVOT)
- NSVT monomorphic and “slow” with a rate < 100 beats/minute
- Long coupling interval with the QRS before the first VA beat
- Absence of R on T phenomenon

What Can be potentially Serious VA in a Phase 1 Clinical trial

- VA associated with a prolongation of the QTc interval or the QRS duration
- VA lasting > 30 seconds
- VA associated with symptoms (dizziness, lipothymia, syncope ..)
- Torsades de pointes
- Polymorphic VA
- Short coupling interval with the QRS before the first VA beat
- R on T phenomenon

Objectives

- The aim of the present report is to review the ventricular arrhythmias observed during a FIM Clinical Trial
- Associated with an intensive ECG program
- The primary objective of the Study being to assess the safety and tolerability of single and repeated ascending doses of a compound compared to placebo when administered to healthy male
- And to discuss the clinical relevance of these findings with relation to Study Drug.

Methods (1): classic Phase 1 design in HV

- ***Part 1 (SAD):*** randomized, double-blind, placebo-controlled, single-dose escalation, alternate crossover design in two cohorts of healthy male volunteers. Seven single doses of study drug planned

- ***Part 2 (MAD):*** single-center, randomized, double-blind, placebo-controlled, multiple-dose escalation, parallel group design in healthy male volunteers. Five dose levels administered once a day for seven days

Methods (2)

- Holter schedule (digital, 12leads) as follows:
  - Screening recording.
  - SAD phase: 2 consecutive Holters, at Day-1 and at Day 1.
  - MAD phase: 5 Holters, at Day -1, then at Day 1, Day 3, Day 6 and Day 7.

In conclusion: 2 Holters for each subject in off-drug conditions (one at screening and one at Day -1), 4 Holters for each subject in in-drug conditions.

Methods (3)

- The 24-hour ECG recordings processed as follows:
  - Holter data were electronically transmitted to an ECG Service Provider
  - Holter analysis performed and Holter analysis reviewed by a Board Certified cardiologist.
  - Holter results were reviewed by the Safety Assessing Committee after each single and repeated dose before going to the next dose.
  - VA occurrence time was compared to individual maximum drug concentrations (Cmax)

Results (1)

- Out of the 124 screened volunteers, NSVT were observed at screening in five Holter recordings (four subjects not randomized and one subject randomized).

- The total number of subjects showing at least one ventricular non sustained run was **10** out of **124** total screened, randomized or non-randomized.

- In **six** subjects out of **10**, the NSVT were observed in off-drug conditions (screening or before dosing). In the other 4 cases the arrhythmias were observed recorded in **only one period of dosing** and long far (more than 12h) from drug Cmax.

Results (2)

- Runs of VA only (> 3 beats)
- Cmax <1h
- Dosing at 8 o'clock a.m. at least

PID	Dose	Study Day	Age (years)	Time of Occurrence
S046	**NR**	**SCR**	**52**	**23:37**
S061	**NR**	**SCR**	**30**	**18:58**
S073	**NR**	**SCR**	**37**	**18:53**
S120	**NR**	**SCR**	**50**	**01:16**
S001	20µg SD	DAY 1	50	08:32 (+1)
S005	**200µg SD**	**DAY-1**	**50**	**10:39**
S110	200µg SD	DAY 1	50	04:40
S117	600µg MD	DAY 6	38	02:12
S128	1200µg MD	DAY -1	34	11:04
S172	**1600µg MD**	**SCR**	**43**	**10:10**

PID: Patient number
NR: Non-randomized
SCR: Screening
SD: Single dose
MD: Multiple dose

SCR and DAY -1 OFF drug conditions; (+1) 1 day after dosing

Chiesi

Results (3)

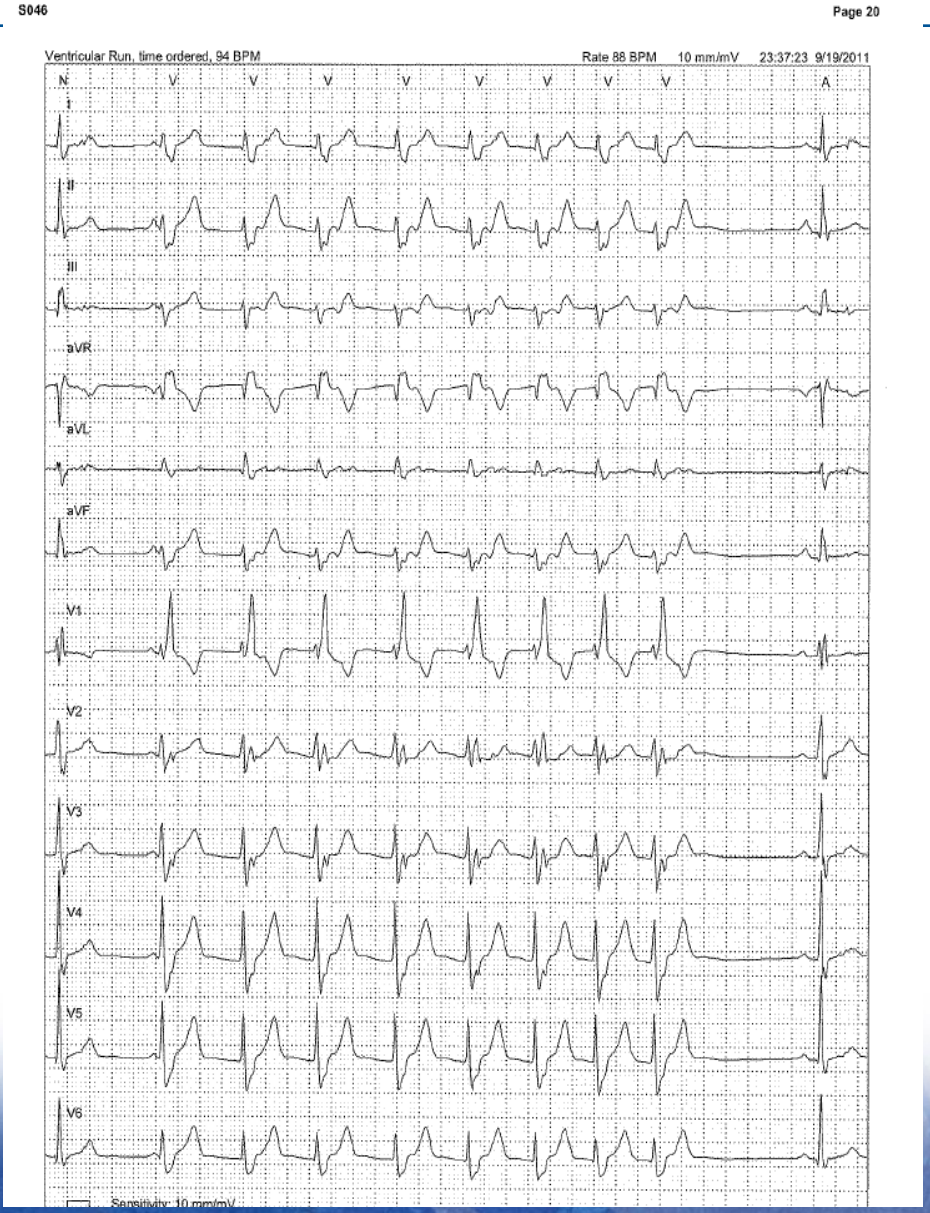
- ECG Characteristics: short runs < 10 beats, monomorphic, 7/10 LBBB pattern, long CI

PID	**LENGTH Beats**	**PATTERN 1 (LBBB, RBBB)**	**QRS AXIS Left, Right**	**PATTERN 2**	**CI First complex ms**	**SHORTEST RR interval ms**
S046	8	RBBB	LEFT	MONOMORFIC	900	540
S061	**3**	LBBB	RIGHT	MONOMORFIC	780	480
S073	**3**	RBBB	RIGHT	MONOMORFIC	720	700
S120	4	LBBB	LEFT	MONOMORFIC	920	340
S001	**3**	LBBB	LEFT	MONOMORFIC	660	360
S005	4	LBBB	LEFT	MONOMORFIC	540	300
S110	**3**	LBBB	LEFT	MONOMORFIC	560	440
S117	4	LBBB	RIGHT	MONOMORFIC	940	300
S128	7	LBBB	RIGHT	MONOMORFIC	1000	440
S172	**3**	RBBB	RIGHT	MONOMORFIC	580	440

LBBB: Left bundle branch block,
Mono: Monomorphic

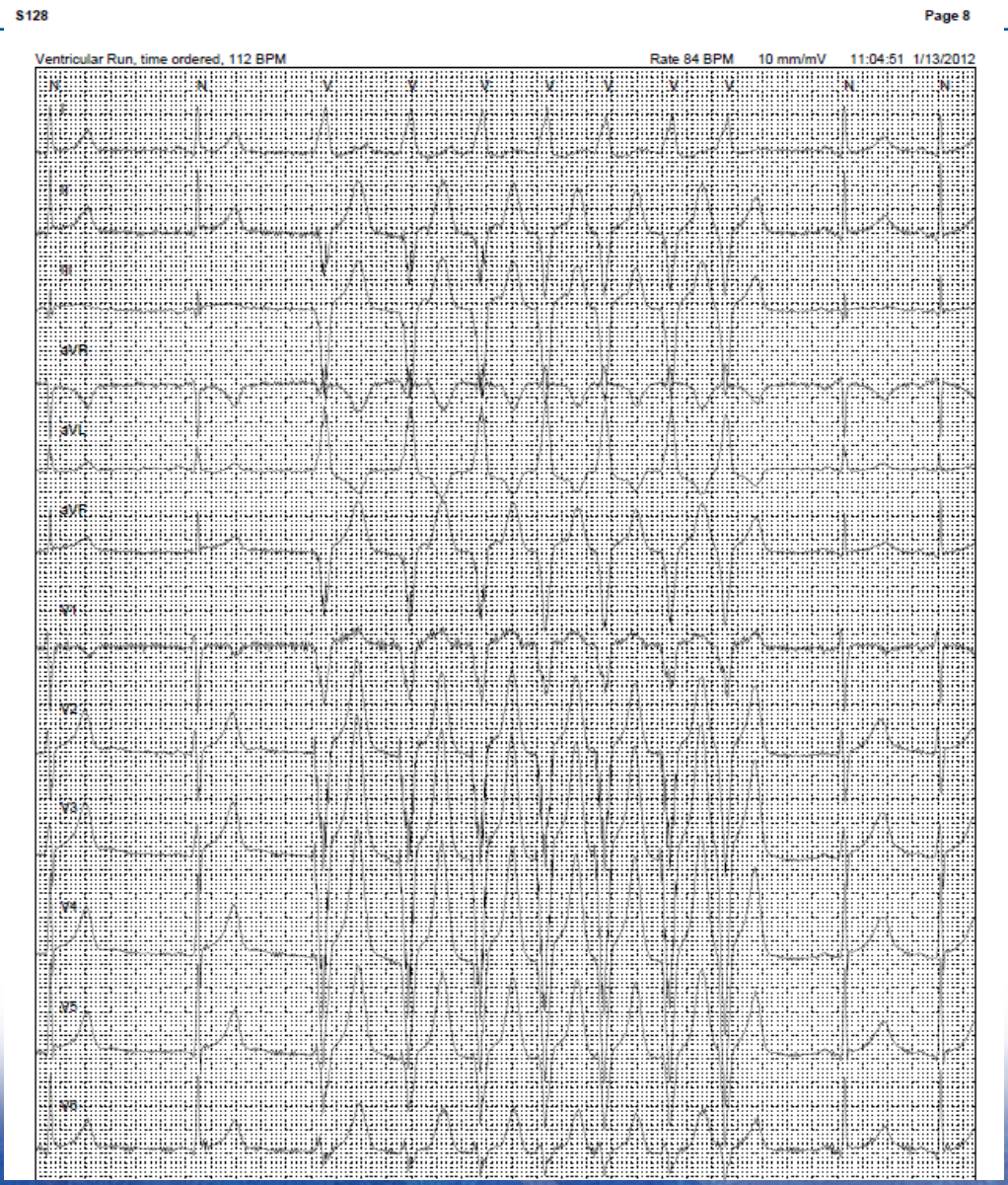
RBBB: Right bundle branch block
CI: Coupling interval

Representative ECGs (1)



S046, Screening

Representative ECG (2)



MAD
S128 Day -1
Off drug

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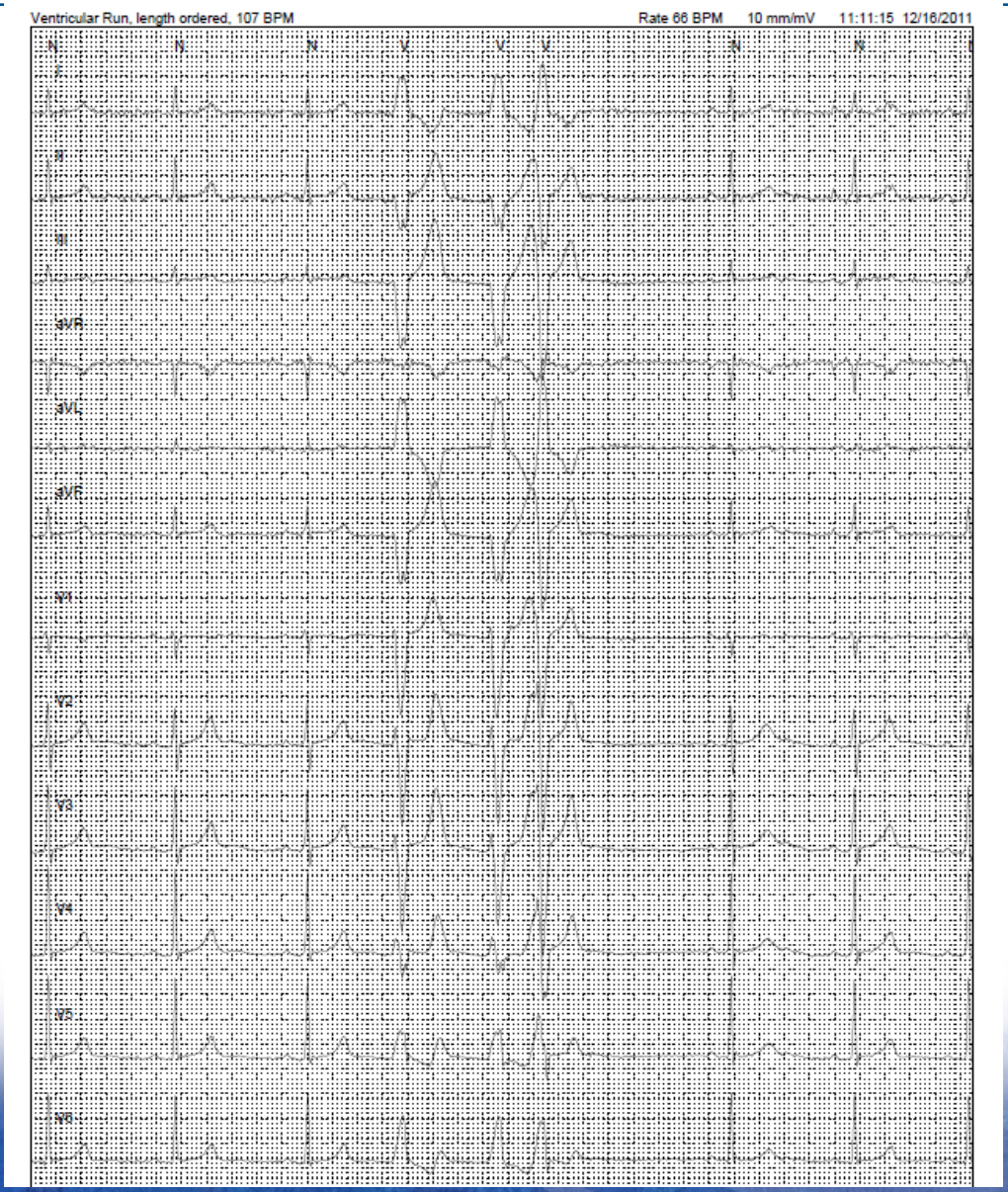
Representative ECG (3)



MAD
S117, Day 6

Conclusions

- The occurrence of ventricular runs was low and in line with the ones reported in the literature in healthy volunteers (10 out of 124, 8.06%).

- Ventricular runs were short and monomorphic, with a predominant left bundle branch block pattern, with a long coupling interval of the first ventricular beats.

- The use of both systematic screening Holter and additional 24-hour recordings before dosing allows determining the “background frequency” of such episodes in off-drug conditions and so permits to detect the real effect in in-drug condition.

Thank you

Let’s pray for the victims in Boston!

God Bless USA

Thanks' for your kind attention!!!!!

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