

# Clinical Investigation data (Tissue Degeneration)

## 1. **Report of clinical investigation study in malignant tumors.**

This document contains the results of a clinical investigation in to **The Effects of Rotational Field Quantum Nuclear Magnetic Resonance on the Degeneration of Tumor Tissue in Terminally Ill Cancer Patients.**

## 2. **Normative references.**

The clinical study was conducted in accordance with EN ISO 14155-1:2003, clinical investigation of medical devices for human subjects part 1: general requirements. (EN ISO 1455-1:2001).

## 3. **Terms and definitions.**

### 3.1 **End point primary**

The end point primary is to determine if the remaining life span of patients deemed terminally ill due to cancer increases as a result of treatment with RFQMR.

### 3.2 **End point secondary**

The secondary end point is to determine if the quality of life of patients deemed terminally ill due to cancer improves as a result of treatment with RFQMR.

### 3.3 **Point of enrolment**

The files of the patients included in the clinical investigation contain a signed informed consent form dated at the time of enrolment in the program. After signing the informed consent form, a pre-treatment MRI scan was made.

### 3.4 Follow up period

Patients were interviewed before and after finishing the treatment; their well being was using a Karnofsky scale, before and after the treatment.

### 3.5 Recruitment

Patients were referred to the clinical investigators mostly by themselves. Patients had to be diagnosed by their own doctors, or one of the investigators as terminally ill and with no other options of treatment left.

## 4. Requirements

### 4.1 General

The clinical investigation plan was prepared in accordance with EN ISO 14155-1 and is included as part of this report.

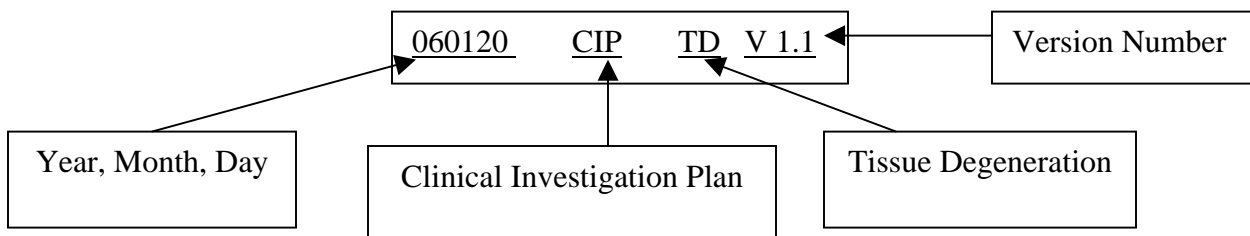
### 4.2 Clinical investigation plan

The clinical investigation plan was developed with scientific optimization in mind. All the diagnosis and evaluation process is fully reproducible. The clinical investigation plan was prepared taking in to consideration all available clinical material on the date of preparation.

### 4.3 General Information

#### 4.3.1 Identification of the clinical investigation plan

The clinical investigation plan was designated a unique identification reference code as follows;



The clinical investigation plan was filed as 050215\_CIR\_TD\_V1.1 and was adopted on Tuesday, 20<sup>th</sup> January 2006 in a meeting of the principal investigator (Dr. Ranjit Kumar), the investigators (Dr. G.S Nayar) and the board of Directors of Scalene Cybernetics Limited.

#### **4.3.2 Clinical investigators, principal investigator, coordinating clinical investigator and investigation centers.**

<b>Investigators' Name</b>	<b>Address</b>	<b>Profession</b>	<b>Position</b>	<b>Role</b>
Dr. Ranjit Kumar	Scalene Centre for Advanced Research and Development (CARD), SCL, Bangalore-560049	Medical Doctor (Aerospace Medicine)	Principal Scientific Officer (Medical), CARD, SCL	Principal Investigator
Dr. G.S. Nayar	118, Devadaru Farm, Vaddrapalya, Hormavu, Bangalore-560043, India	Medical Doctor (Gen. Medicine)	Director, Ojus Healthcare, Bangalore	Investigator

The investigation was conducted at the Centre For Advanced Research and Development (CARD) in Bangalore, India.

Pre-treatment diagnosis and after treatment evaluation were done by the chief investigator and at two diagnostic centers: CLUMAX and Elbit. The patients themselves provided pre-treatment clinical laboratory reports. Where not available, the same were ordered by the Investigators.

#### **4.3.3 Sponsor**

Scalene Cybernetics Ltd, Seegehalli Main Road, Virgonagar, Bangalore, India sponsored the clinical investigation.

#### **4.3.4 Monitoring Arrangements**

The treatment procedure consisted of 60 minutes daily treatments during 28 consecutive days. During treatment, patients were observed by one of the investigators and a qualified nurse. Interviews with the clinical investigators were conducted on a weekly basis. Source data are based on the MRI's was being taken by the diagnostic centers. The investigators for accuracy, upon receipt, checked the radiologist's reports.

#### **4.3.5 Data and quality management**

The results of the individual patient files are summarized in an excel spreadsheet file designated 081107\_PatDat\_Tumor. This file was checked for accuracy by the principle investigator and a member of the Royal Dutch Institute of Certified Auditors (NIVRA). Thereafter, the patient files were archived in a sealed box. This archive will be retained at the library of the sponsorer according to the standard procedures of the sponsorer for a period of 5+2 years and will then be destroyed in accordance to the norms specified for destruction of archives. A protocol of the archival destruction will be finally added to the clinical investigation file.

#### **4.3.6 An overall synopsis of the clinical investigation**

The clinical investigation was conducted under the following protocol;

- Patients were referred to the clinical investigation by the patients themselves or independent doctors who were aware of the clinical investigation, taken in to account the exclusion and inclusion criteria. Patients with no other options were accepted for the trial and had a limited life span. After signing an informed consent from patients, they were subjected to clinical laboratory tests and a pre-treatment MRI. With this MRI, the location of the tumor (s) was established and filed in the patients' file. This MRI was also used to confirm the patient's radiological condition. Patients' prognosis is determined using a special life – expectancy-predicting protocol based on the published paper “Determining prognosis in patients with advanced and incurable cancer<sup>1</sup>”. The model was adjusted to take in to account the latest insights.

- Based on the MRI, the radiologist would perform CT guided surface marking for identifying and localizing the tumor.
- A MRI of the affected region or the whole body MRI is done depending on the type and severity of the disease. The proton density of each of the tumor mass all over the body is obtained using a 3D-PD sequence from a magnetic resonance imaging device.
- The radiologist and the oncologist will decide on the primary site of the cancer, and decide on planning the treatment regime, i.e. the tumor to be exposed to Cytotron treatment.
- The radiologist will then prepare the “target planning films”, this is derived from the 3D – PD sequence of the MRI, that shows the core of the tumor mass and then he will position as many guns as required to be fired depending on the disease and the type of molecules to be permeated. A specially trained medical doctor then prepares the required treatment schedule from the data obtained from the oncologist and the radiologist. The tumor is identified and marked on the patient’s body under Computer aided tomography guidance. These marks are transferred to a template for future use during the start of the Cytotron treatment. The investigators check the template
- Based on the proton density, the dosimetry was prepared by a RFQMR technologist and approved by one of the investigators.
- This dosimetry was then uploaded to the Cytotron. Either the principal investigator or the co-investigator checked correct uploading.
- On the day of the exposure, the patient is made to lie down on the machine and is rolled in; the RF-guns now focused at the target using a laser guided system with the help of the template. The technician who operated the control unit would then read out aloud the patient’s name from the monitor and the nurse would check the name by identifying the patient and checking the name on the template. If the nurse and the technician are satisfied that the patient’s identity is sufficiently established, the technician would start the Cytotron. This procedure was often observed by one of the investigators.

- The exposure is for Y-hours each day for Z-days. Y is dependent on the tumor volume and other parameters like the histopathology of the cancer cell type and Z is the course or number of cycles of RF exposure. The periodic assessment is done using ultrasound or CT/MRI. The volunteer patients in this trial were all declared as terminally ill with multiple tumors by their treating doctor. Hence the exposure time and number of exposure were uniformly fixed as one hour daily and for twenty-eight consecutive days respectively.
- At the end of the treatment schedule, the nurse helped the patients off the Cytotron and would note down any subjective feelings experienced by the patient during the treatment.
- Patients were assessed periodically depending on their disease status. Generally, assessment was done and recorded once in a week. Once in a week, the patients were interviewed by the principal investigator and their quality of life were observed and considered.

#### **4.3.7 Approval and agreement to the clinical investigation plan**

The clinical investigation plan was accepted on 20<sup>th</sup> January 2006 by Sponsor represented by Dr. R.V. Kumar, Managing Director and Dr. Ranjit Kumar, and Dr. G.S. Nayar, Investigators of the project and was subsequently approved by the board of Directors of Scalene Cybernetics Limited.

#### **4.4 Identification and description of the medical device to be investigated**

The Cytotron<sup>®</sup> 864 is a long body, wide bored machine with 864 guns, with near field antennae and parabolic reflector delivery system. The device is capable of producing a wide range of dosimetry, involving multiple modulations in both fixed and variable proton density dosimetry, thus able to tackle systemic disorders in the years to come. Appropriately modulated multi-harmonic RF signals in the lower end spectrum can be used in altering the cell signaling process using the Trans Membrane Potential Pathways (TMP). Generically known as Rotational Field Quantum Nuclear Magnetic Resonance (RFQMR), is a technology that is intended to deliver highly complex quantum instantaneous nuclear magnetic resonance beams in the radio frequency bands and its harmonics ranging from 3 HZ to 300 MhZ in the presence of high instantaneous magnetic field

between 1mT to 6T, with a near field delivery using specialized antennae. Trans-membrane or TMP pathways play an important role in the protein synthesis signaling. Altering this pathway can synthesis many different protein or stop their synthesis, that can be exploited in the treatment of cancer.

#### **4.4 Preliminary investigations and justification of the study**

The study of the interactions between electromagnetic fields and living matter has become a fertile field for research in the last century, even though these phenomena have been empirically observed by various civilizations since ancient times. Considerable experimental evidence today points to the possibility of modulating biological functions and structure in a controlled way by applying electromagnetic fields and vice versa, the possibility of detecting and measuring endogenous electrical currents in living organisms and their components.

There are three types of electromagnetic effects on living matter: **Ionising effects** (as in X-rays and radiotherapy), **thermal effects** (as in RF ablation) and **non-thermal non-ionising** effects such as in RFQMR therapy. Ionising effect knocks off electrons from the atoms in the molecules, thus causing uncontrolled destruction, thermal effects induce an entropic disorder in the target, until at adequate frequencies and power levels hyperthermic destruction occurs. The non-thermal non-ionising effects are not the result of the transfer of erratic movement by means of an increase of kinetic energy, but rather, in line with the theories of the coherence of condensed matter, they can transmit information that would produce order in the bio-structures involved. The information content of the RFQMR beams would depend strictly and specifically on the waveform, the string of waves, the time sequence of their modulation pattern, spin around the target, rotation, radiation and delivery. In fact, specific variations in the configuration and temporal exposure patterns of RFQMR radiation can produce highly specific biological responses, similar to many powerful pharmaceutical products. These effects are attracting considerable scientific interest mainly because a Radio Frequency beam is easily modulated and thus is an excellent means for the transmission of information. The low end RF spectrum can provide precise command and control.

Based on these concepts, it is reasonable to consider patterns in living matter that take in to account the electromagnetic components of biological structures. Every cell, for instance, is made up of biological and chemical components that can be described in simpler and simpler terms down to the cell's elementary molecular constituents. But the cell itself and its internal and external interactions can also be considered in terms of electric and electromagnetic interactions and relationships. Numerous experimental works have shown the possibility of modifying and controlling the selective permeability of the cell membrane by transmitting specialized resonantly rotating RF waves. This leads to the possibility of verifying the specific reactions of healthy cells compared to the reactions of pathological cells and subsequently to select target cells on which to act for clinical purposes. **Pathological cells are different from healthy cells due to a different tissue composition** (that affects its proton density, permitivity, conductivity, etc.).

On these bases, we have noted the modulation of some cell functions, from ionic membrane pumps to many cytoplasmic enzyme reactions, including those connected with cell replication. From these observations it has been seen that these effects can be obtained from the non-ionising, non-thermal RFQMR beams. Along this line, preliminary observations performed in vitro have shown alterations of the cell morphology, the halt to proliferation, fusion and necrosis in lymphoblastoid cell lines and some neoplastic lines subjected to specifically modulated RF radiation.

So we hypothesized as follows;

It is known that the chromosomes, following the cell signaling received as a result of the variations of potential (-70 to -90 mV normal, -40 to -60 when infected, -20 to -30 in cancer and 0 when dead) in the cytoplasmic membrane, activate through electromechanical effects (also called stress responsive), the emission of messages by the genes that regulate cell dynamics for normal cell functions or for the mitochondrial activities for ATP production. An electrical equivalent circuit composed of a Zener diode attached to the base of a bipolar transistor is offered as a model for the operation of the mitochondrion. The Zener diode represents the on/off pulse operation of some cell functions, the combined circuit impedance of the glycoproteic sensors present on the mitochondrial membrane, and the transistor represents the ATP activation process.

It is supposed that the excessive production of the ATP is related to an alteration of the glycoproteic sensors present on the mitochondrion membrane with consequent lowering of the impedance that in turn does not discriminate between the signals in frequency and activates the production of ATP in an almost continual way. The cancer cell would therefore go in to mitosis due to the excess of ATP. RFQMR radiations are used to act on the mitochondrial membrane, increasing the impedance of the glycoproteic sensors through the lengthening of the polyglycidic chain. The spin of the RFQMR field is used to interfere with the communication between the genes and the protoplasmic glycoproteic complexes involved in the promotion of cell mitosis.

It is thought that the impedance of the mitochondrial membrane of the messages coming from the genes increase with RFQMR treatment and with increase in malignancy (the highest impedance of undifferentiated tumors). This is related to a greater alteration of the sensors of the undifferentiated tumors and therefore to their greater predisposition to the bond with polyglycidic chains. The **undifferentiated neoplastic cells**, because of the high impedance induced on the mitochondrial membrane by the RFQMR radiation exposure, it stops producing ATP and therefore 'possibly' **enters in to necrosis**. Following the exposure, the undifferentiated neoplastic cells have an impedance which is still sensitive to some signaling coming from the chromosomes promoting the normal production of ATP, so the cells change their state of mitosis; however they continue to live in a quiescent state (vegetative form of life) until it finally attains apoptosis. The responsible protein-signaling pathway is targeted to be P 73 (a silent partner of P 53) as P 53 is mutated to start with. The normal cells are not influenced by the RFQMR radiation exposure as the impedance of their mitochondrial sensors are not modified and remain sensitive to signals that arrive from the chromosomes for the activation of ATP synthesis (the proton density or the number of hydrogen atoms of the tumor cells are different from that of normal tissues). There is evidence that thoracic tumors exposed to RFQMR have undergone necrosis in some cases and apoptosis in other, sometimes both types of cellular destruction is seen, with apoptosis being more pronounced.

#### 4.5.1 Literature review

- Levengood W. Cytogenic variation induced with a magnetic probe. Nature 1966; 209: 1009 – 1013.

- Salvatore J, Blackinton D, Polk C, Mehta S. Non-Ionising electromagnetic radiation: A study of carcinogenic and cancer treatment potential. Review on Env Health 1994; 10: 197 – 207.
- Watson J, Parish E, Rinehart C. Selective potentiation of gynaecologic cancer cell growth in vitro by electromagnetic fields. Gyn Oncol 1998; 71:64-71.
- Williams C, Markov M, Hardman W, Cameron I. Therapeutic electromagnetic field effects on angiogenesis and tumor growth. Antican 2001; 21: 3887-3892.

#### **4.5.2 Pre-clinical testing**

Before start of the use of the device, the device was tested for electrical safety by the engineers at the Center for Advanced Research and Development (CARD). An independent test was conducted by the Electronics and Radar Development Establishment (LRDE), Ministry of Defence, Government of India, to establish the safety in accordance to the recommendations of the International Commission for Non-Ionizing Radiations Protection (ICNIRP). It was observed by the agency that both electric and magnetic field emissions from Cytotron are well below the hazardous levels specified by ICNIRP for the measured frequency band and thus safe to be used on biological systems.

#### **4.5.3 Previous clinical experience**

This being the first of its kind trial in using the device to halt mitosis in neoplastic cells; there has been no previous clinical experience. However the use of the technology in clinical research to regenerate cartilage is well established. As the technique deals with use of Cytotron device in altering the TMP pathway in initiating specific protein synthesis, the device can be applied for the intended application.

#### **4.5.4 Device risk**

The engineers at CARD as well as third party scientists from LRDE, Government of India, evaluated the device risk from the point of view of performance and patient safety. The device failure mode was assessed by the use of FMEA mode of analysis. There were no adverse effects reported by the investigators.

#### **4.5.5 Objectives of the clinical investigation**

The objectives of this clinical investigation are as follows:

- Slowdown or stop mitosis (cell division).
- Cause severe damage to the cancer stem cells (undifferentiated cancer cells) to prevent metastasis (migration and spread of cancer).
- Reduce pain, improve appetite, aid in weight gain and thus improve quality of life.
- Finally, achieve tumor cell apoptosis (natural programmed cell death) and eliminate the disease.

#### **4.5.6 Design of clinical investigation**

- For ethical reasons it was decided not to undertake a double blind, parallel design or a study with a control group. Increased life span and proof of increased well-being is sufficient confirmation of the claim being made in this study.
- Bias could exist at the initial evaluation for end points at the end of the treatment. The increased life expectancy could be biased by either the model being used or by the subjective factors going in to the model. The model is widely used in hospices for planning purposes and is deemed reliable. The model is multivariable and takes also in to account objective variables as “white blood cell counts” and “lymphocytes” and results from the clinical examination, the influence of subjective factors is limited. Also, the patient’s doctor diagnosis has to be confirmed by a MRI scan and the diagnosis by an independent radiologist. However, it appears from the statistics that the results from the evaluation at the end of the treatment vary consistently with the type of cancer. This is an indication that bias from patients wanting to please the doctor is limited.
- The first end point, extended life span was chosen because it is one of the clearest indications the treatment has effect. Biological effects of radio fields and nuclear magnetic fields are well documented in literature. It is however still unclear how precisely these effects are generated. A patient with a diagnosed cancer and who has exhausted all possible

treatment modalities has according to the palliative prognostic score rating on average maximum 100 days to reach palliative stage. The palliative state is supposed to endure maximum of 45 days. We decided if there was any very clear signal that in patients that were treated, the life span extension was considerable, this end point has to be considered valid. The actual average life span of the treated patients was 317 days. This is considerably higher than the average maximum life expected life span of 145. if compared to the average palliative prognostic score rating the results are 317 days as compared to the expected 115 days of the actual patients participating in the clinical trial.

#### **4.19 Test equipment**

Test equipments used during the clinical investigation are as follows:

- Magnetic resonance imaging system: Siemens with TIM, 1.5 T MRI scanner device.
- Cytotron<sup>®</sup> Rotational Field Quantum Nuclear Magnetic Resonance. Device.

#### **4.20 Inclusion criteria**

The inclusion criteria are patients deemed terminally ill with cancer with no other known treatments left.

#### **4.21 Exclusion criteria**

The exclusion criteria are similar as for a MRI scan (removal of anything containing metal, hearing aids, hairpins, bra, body jewellery, necklace, etc.).

#### **4.22 Point of enrolment**

The point of enrolment is the signing of the informed consent form by the patient.

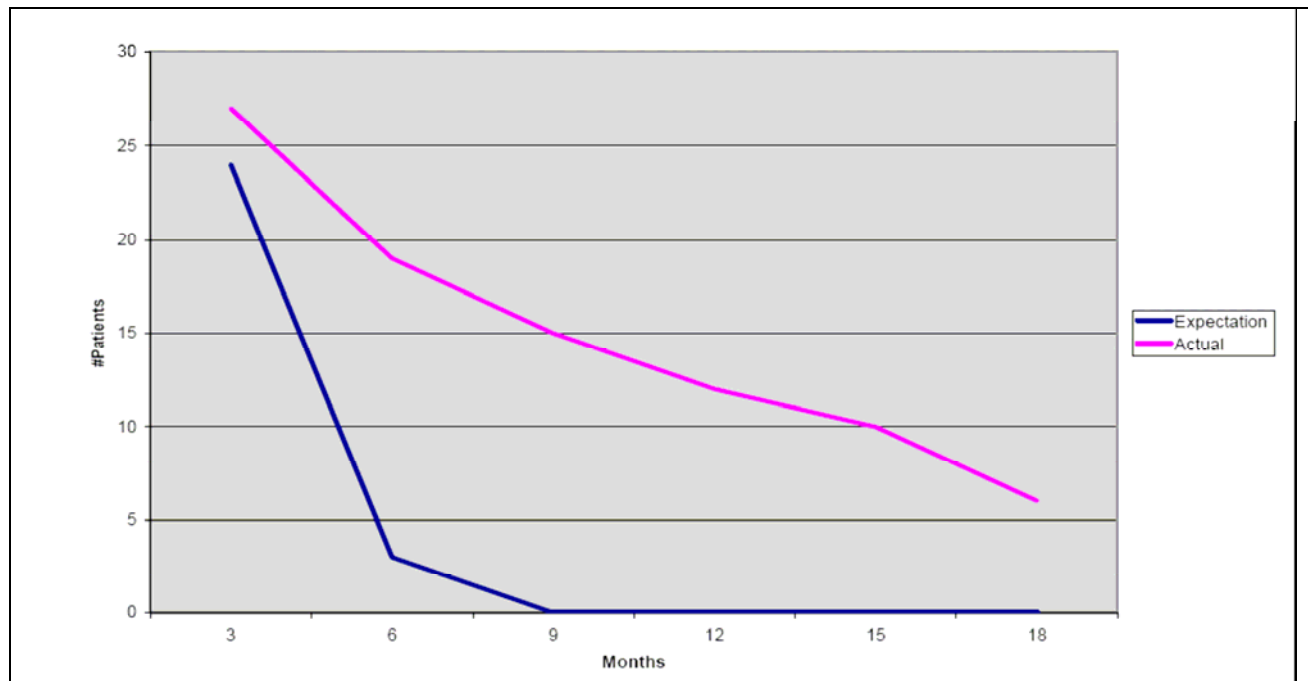
#### **4.23 Role of other factors**

None, all patients were terminal cancer patients and were not on any kind of medications or other treatment other than Cytotron exposure.

#### 4.24 Population enrolment

	Expectation	Actual	Percentages	
<b>No. of patients with informed consent</b>	45	45		
<b>No. of patients that completed treatment</b>	36	32	80%	71%
	Expectation	Actual	Months	
<b>Three (3) month survival post treatment</b>	24	27	3	84%
<b>Six (6) month survival post treatment</b>	3	19	6	59%
<b>Nine (9) month survival post treatment</b>	0	15	9	47%
<b>Twelve (12) month survival post treatment</b>	0	12	12	38%
<b>Fifteen (15) month survival post treatment</b>	0	10	15	31%
<b>Eighteen (18) month survival post treatment</b>	0	6	18	19%

#### Survival probability



- During CIP, it was estimated that 20% of the patients would leave the program due to their illness or for other reasons. Of the enrolled patients, 71% completed the treatment. Two patients (4%) died during the treatment, 31% left the treatment prematurely for reasons of their own. The patients who died during the treatment are considered as having completed the treatment and are accounted for in the survival statistics. No adverse effects that were not anticipated have occurred during the clinical investigations.

- The objective of this investigation was to prove that RFQMR has a positive effect on the life span and well being of terminal ill cancer patients. A sample size of 35 patients was deemed as sufficient because the only discriminating variable is the remaining expected life span. For capacity reasons, the clinical investigation had to be spread out over a period of approximately 12 months.
- The outcome or the interpretation of the results was not affected in any other way than was foreseen. We emphasize we were dealing with terminally ill patients.
- The investigation was closed in November 2007. the average expected life span at the moment of the design of this clinical investigation was 75 days without RFQMR treatment. None of the admitted patients was expected to live beyond a period of 225 days (three times the expected life span). Patients were followed during the period after treatment until their death. For the purpose of this study, it is assumed that the patients who are still alive died at the end of the study period being 15/11/2008. it is remarkable that 13 patients out of 32 lived longer than one year after beginning the treatment.
- Patients received no other medication than rescue medication (analgesics), symptomatic treatments and dietary supplements.

#### **4.25 Statistical Considerations**

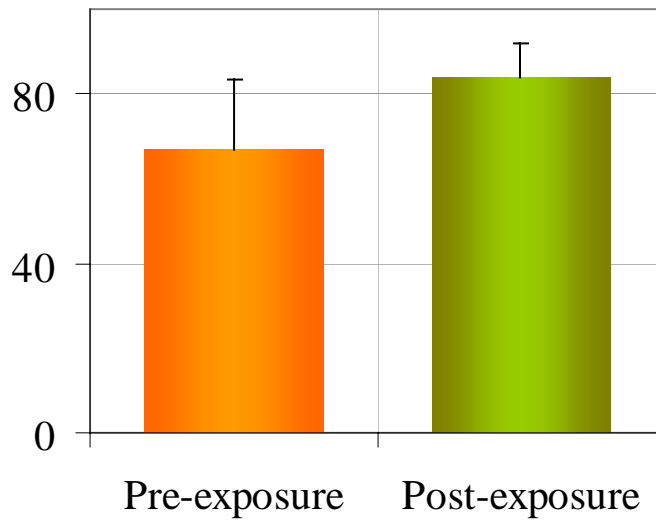
First, data were examined for normality of distribution using Shapiro Wilk's 'W' Statistic. Survival data showed significant departure from the assumption of normality. Therefore, to compare the expected and observed survival time, Wilcoxon matched pairs test was employed. For 'K' scores, a paired 't' test was used.

Level of significance was set at  $p < 0.05$ . However, exact significance is annotated in the tables presenting the outcome of analysis.

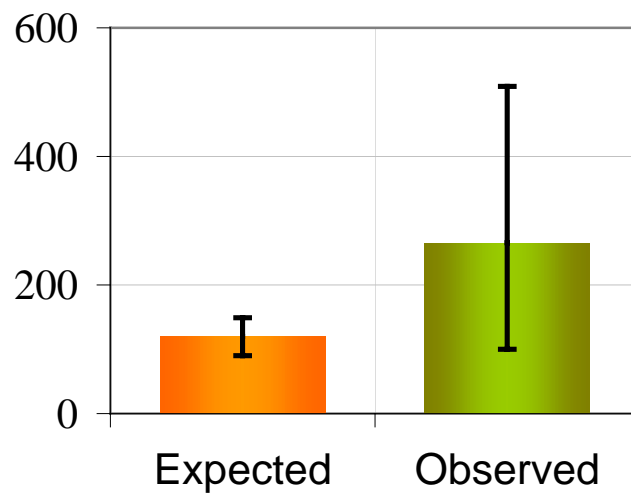
#### 4.26 Results

A significant ( $T=58$ ;  $P = 0.0001$ ) increase in survival time was noted. Median value of actual survival was 120 days (lower & upper quartiles 90 & 149 days). Median value of actual survival was 256 days (lower and upper quartiles 100 & 509 days).

'K' scores increased significantly ( $t = -6.93$ ;  $p = 9.06 \text{ E} - 08$ ) from its pre exposure value of  $67 \pm 17$  to  $84 \pm 8$  after exposure to RFQMR.



**Fig – 1; Variation in 'K' score with exposure to RFQMR. Error bars represent +1 SD.**



**Fig-2; Expected and actual survival in day. Error bars represent upper and lower quartiles.**

#### **4.27 Deviations from the clinical investigation plan**

In May 2006, it was decided to adjust the remaining life span model based on new insights as published in the Indian Journal of Medical and Pediatric Oncology and to adjust the predictions of the previous model.

#### **4.28 Amendments to the clinical investigation plan**

There were no amendments to the clinical investigation plan.

#### **4.29 Adverse events and adverse device effects**

There were no adverse events or adverse device effects.

#### **4.30 Early termination or suspension of investigation**

There was no early termination or suspension of the investigation. The clinical investigation was completed as intended.

#### **4.31 Publication policy**

No publication will be authorized before the CE mark as a class 2A medical device is obtained.

#### **4.32 Case report forms**

Sample case report forms for one patient is attached with this report

#### **4.33 Raw Data used for analysis in this report**

The Raw Data used in conducting the analysis is attached to this report.

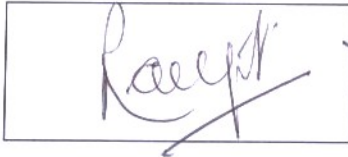
Signatures:

**Principal Investigator**

**Dr. Ranjit Kumar**

Date Signed

6/11/2008

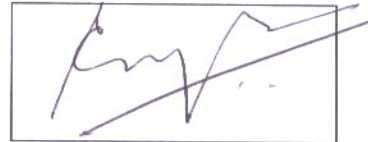


**Investigator**

**Dr. G. S. Nayar**

Date Signed

6/11/2008



**Sponsor**

**Dr. Rajah Vijay Kumar**

**Chairman and Managing Director**

**Scalene Cybernetics Limited**

Date Signed

6/11/2008

