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Research Article

Phase-III Clinical Trial with an Intravasal Once Injectable Non-Hormonal Male Contraceptive-Reversible Inhibition of Sperm under Guidance (RISUG)

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ABSTRACT

Objective: To obtain sufficient evidence about the efficacy and safety of an intravasal, injectable and non-hormonal male contraceptive RISUG® in a large number of healthy subjects.

Method: Design-Prospective, straight, open-labelled and non-randomized, multi-center hospital-based phase-III clinical trial; Setting-Family planning clinics; departments of urology and surgery; Patients-Total of 303 healthy, sexually active and married male subjects (aged 25-40 years) and their healthy and sexually active wives; Injection(s)-A 60mg of RISUG® injected per vas deferens in a vehicle of 120 µ l dimethyl sulphoxide to male subjects only; Main outcome measure(s)-Overall efficacy of RISUG® with respect to achieving azoospermia was 97.3% and based on pregnancy prevention was 99.02% without any serious side effect.

Results: Subjects achieved azoospermia ranged from 76.5% to 96.5% after 21 days of RISUG injection at various centers which reached to the highest level of 92.7%, 96.3% and 96.6% at 6 months post injection at Jaipur, New Delhi and Udhampur centers respectively and remained same till the last follow-up reported. In remaining two centers i.e. Kharagpur and Ludhiana, the subjects achieved 100% azoospermia at 6 week and 2.5 months post-injection respectively and the trend remained same till the last follow up reported. No serious adverse effect was reported both in RISUG® injected subjects and their wives till last follow up reported.

Conclusion: RISUG® is a safe and highly efficacious male contraceptive without any serious side effects.

Keywords: Azoospermia; Male contraception; Phase-III clinical trial; Pregnancy; RISUG

INTRODUCTION

With an ever-increasing world population, there is an urgent need to develop modern methods of male contraception for population control. Even though vasectomy is quite effective as a contraceptive measure, some major limitations of this method call for the development of improved techniques. An ideal male contraceptive approach should have minimally invasive drug delivery system with a one-time injection, long-term effectiveness with negligible side-effects and the option of reversal. To achieve these goals, a novel male contraceptive approach of Reversible Inhibition of Sperm under Guidance (RISUG®) has been developed, which has the potential to become for mass use as once injectable and reversible male contraceptive method [1-5]. Significant features of this method include localized injection and no detectable interaction with other body parts unlike the hormonal injectable contraceptives.

RISUG® is based on the injection of a polymeric agent, Styrene Maleic Anhydride (SMA) in a vehicle of Di-Methyl Sulph Oxide (DMSO) [6], into the lumen of the vas deferens. Multiple factors contribute to RISUG®-mediated fertility control. First, the inherent negative surface charge on spermatozoa is disturbed by a charge mosaic generated by the injected drug that causes rupture of the acrosomal membrane. The subsequent leaching of enzymes (acrosin, hyaluronidase, etc.) results in the loss of fertilizing ability of spermatozoa. Secondly, the acidifying property of the SMA also adds to this effect and the number

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of spermatozoa passing through also reduces (azoospermia or severe oligozoospermia) [4-6].

Studies conducted on albino rats [7] and rhesus monkeys [8] demonstrated the efficacy, and toxicological and teratological studies established the safety of this approach [9-15]. Results of phase-I and II clinical trials indicated that the injection of DMSO and DMSO-SMA mixture into the lumen of the vas deferens is a safe procedure with no long-term adverse effects [16,17]. Genotoxicity, mutagenicity and carcinogenicity studies were also conducted with RISUG and the data collected was reviewed by an Indian Council of Medical Research (ICMR) Committee of experts. The committee concluded that the RISUG is a safe contraceptive in terms of mutagenicity, genotoxicity and carcinogenicity potential [18]. Efficacy, safety and reversal studies were also conducted on langur monkeys (1995-2005). Functional azoospermia reversal within a short period of time [19] and repair of exfoliated epithelium (due to vas occlusion by SMA) after 150 days of reversal [20,21] were observed. Based on repeated vas occlusion and non-invasive reversal carried out in langur monkeys, it has been reported [22,23] that the RISUG has the feasibility of a spacing method for contraception using the SMA. Additionally, no damage to the accessory reproductive organs in langur monkeys [19] and feasibility of reversal even after long-term use (540 days) without any adverse side-effects [20] were found. The similarity in the reproductive endocrine and exocrine profile of langur monkeys and humans [24-27] offered strong possibility for a similar response of the drug in humans. Restricted phase-III clinical trial similarly indicated that RISUG® injection is a safe clinical procedure with no significant adverse health effects and has high sustained contraceptive efficacy [28]. Based on the observations of restricted phase-III clinical trial, it was decided to conduct phase-III clinical trial with RISUG® to obtain sufficient evidence about its efficacy and safety in a large number of healthy subjects.

MATERIALS AND METHODS

Study design and participants

It was a Prospective, straight, open-labelled and non-randomized, multi-centre hospital-based phase-III clinical trial. Carried out at five different centres (New Delhi, Udhampur, Ludhiana Jaipur, and Kharagpur) located in different states of the country and coordinated by the Indian Council of Medical Research (ICMR, New Delhi). Permission to conduct phase-III clinical trial was granted by the Drugs Controller General India (DCGI) and approved by the institutional ethical committees of the respective centres (Protocol No: RISUG-III-108-2007). Enrolled subjects were from amongst those coming to family planning clinic and department of urology or surgery for vasectomy or No Scalpel Vasectomy (NSV). Detailed eligibility criteria for subject enrolment are described (Supplementary Table 1). All subjects provided written informed consent to participate in the study.

Procedures

General examination of the male subjects and their wives was undertaken to establish a set of 'normal' characters and values for the individual so that any changes in the health status post RISUG® injection can be properly assessed. This included collection of data (pre and post-injection) on ultrasound of vital organs, scrotum (males) and lower abdomen (females), chest X-ray, blood, semen (males) and urine examinations. A minimum of two semen samples after 3 days of abstinence (each time) were obtained from all the enrolled male subjects for pre-injection data on count, density, morphology, motility and viability of sperms. Information about demography, current contraceptive use, clinical and reproductive profile was obtained from male subjects and their wives through a pre-designed proforma. Haemogram, liver and kidney function tests were performed on the blood samples and urine test by standard routine methods. Semen samples were analyzed as per the World Health Organization method manual. Testicular size was measured and recorded using an orchidometer and ultrasound.

Subjects that had cleared the preparatory medical examinations were cautiously administered the drug. Place of injection was a hospital or a health centre with properly equipped and staffed minor operation theatre. Following a "Three-Finger Technique" [29], RISUG® (60 mg SMA) was injected through pre-filled syringes in each vas deferens (120 µ l/injection), one by one, under local anesthesia [16,17]. (See "Injection Procedure" in supplementary information for details). Any complication arising during the injection procedure was also recorded and subjects were advised to use condom till 2 months post RISUG injection.

On the 3rd day post-injection, subjects were monitored keeping the following complications in view-pyrexia, inflammation (local and reproductive system), infection (local, reproductive system, and urinary system), persistent pain in the scrotal region (low grade: Awareness of the pain, but easily tolerated; moderate: Discomfort enough to cause interference with usual activity; severe: Inability to carry out usual activity), urethritis, vesiculitis, cystitis, prostatitis, epididimytis, orchitis, dysuria, urinary retention. To measure extent of post-operative scrotal swelling, a ten-point visual analogue scale was used.

Medical examinations were conducted on each subsequent visit that is on the 7th and 21st day, 1½, 2½, 4, 5 and 6-months post-injection. First and second post-injection semen samples were obtained in the 3rd and 6th week respectively. Afterwards, semen samples were obtained at 2½, 4, 5 and 6 months. Information on count, density, morphology, motility and viability of sperms was obtained again for comparison. Afterwards all the subjects were subjected for all clinical and laboratory examinations once in 6 months that include Liver Function Test (LFT), Kidney Function Test (KFT), hemogram, urine test, blood sugar, ultrasound, chest X-ray and semen analysis up to seven years post injection.

Wives of all subjects were interviewed 6-monthly for recoding of reproductive profile and clinical and laboratory examinations (haemogram, LFT, KFT, urine) along with their husbands. All the wives were also subjected to ultrasound and X-ray examination on each visit to ruled out the pregnancy and any other abnormality. The wives who were having gestational sac under ultrasound were gynecological extensively examined and hormonal tests were also performed. Once the pregnancy is confirmed the women were advised to go for MTP. To rule out failure of the drug, two semen analysis of the husband of the pregnant woman were undertaken, one at the participating centre and, another at Referral Centre. Trial was initiated in July, 2007 and deferred in September, 2008 due to non-availability of the drug. Trial resumed in March, 2012.

Outcomes

For an individual, the outcome was defined as 'successful' if.

- Semen sample showed azoospermia or immotile/dead parts of spermatozoa/non-functional sperms/severe oligozoospermia within 2½ months of RISUG® injection.
- Monthly semen samples thereafter showed the above-mentioned

semen characteristics.

- No pregnancy attributable to a period following the onset of above-mentioned semen characteristics and withdrawal of condom.

Statistical analysis

Descriptive statistics were used for analysis of demographic profile, clinical examinations, semen analysis, hematological and biochemical investigations of the male subjects. Similar analysis was done for data of wives of the subjects. Identity matched data were arranged for pre and post-injection follow-up visits longitudinally. Continuous variables were described as means, medians and standard deviations. Categorical variables were described as frequencies and percent.

For continuous data, one-way ANOVA with repeated measurements was applied to test the significant difference between pre and post-injection observations over time. In case of violation of assumption of homogeneity of variances, Greenhouse-Geisser correction was applied. For categorical data, Friedman test/Kruskal-Wallis test was applied to test statistically significant difference during follow-up visits. All the analysis were performed using Statistical Package for the Social Sciences (International Business Machines Corporation. Released 2017. International Business Machines Corporation Statistical Package for the Social Sciences Statistics for Windows, version 25.0. Armonk, NY: International Business Machines Corporation).

RESULTS AND DISCUSSION

A total of 784 subjects were contacted at all the five participating centres and out of that, 358 subjects full filled the inclusion and exclusion criteria and only 315 subjects came for the RISUG injection. Out of 315 subjects who received RISUG injection, 5 subjects were lost to follow up and 7 subjects showed protocol violation. Therefore, the present analysis has been carried out on 303 subjects only (Supplementary Figure 1). Demographic characteristics of subjects and their wives are given in Supplementary Table 2.

Efficacy of RISUG

Overall visit-wise efficacy of RISUG® in male subjects is shown in Figure 1. At 21 days post-injection, 77.2% and 13.5% subjected achieved azoospermia and oligozoospermia with non-motile sperms respectively. Afterwards the percentage of the subjects achieving azoospermia increased to 97.2% at 6th month post-injection and reached to the highest level of 97.3% after 1-year post-injection. This trend continued till the last follow up reported Figure 1.

Subjects achieved azoospermia ranged from 76.5% to 96.5% after 21 days of RISUG injection at various centres which reached to the highest level of 92.7%, 96.3% and 96.6% at 6 months post injection at Jaipur, New Delhi and Udhampur centres respectively and remained same till the last follow-up reported. In remaining two centres i.e. Kharagpur and Ludhiana, the subjects achieved 100% azoospermia at 6 week and 2.5 months post-injection respectively and the trend remained same till the last follow up reported. The centre-wise difference in achievement of azoospermia was statistically significant (p=0.00053).

A total of 8 pregnancies were reported but 4 of these pregnancies had social cause as their husbands were showing persistent azoospermia and remaining were due to method failure (0.3%, n=1) and drug failure (0.98%, n=3). Therefore, the overall efficacy of RISUG® in terms of achieving azoospermia was 97.6%. And, overall efficacy based on the occurrence of pregnancies due to drug failure was 99.02%.

Safety of RISUG injected subjects

Clinical examination of male subjects: Clinical examination showed that no serious adverse effects were noticed in terms of pyrexia, local inflammation at the site of injection and reproductive system and infection of urinary system (Figure 2). Even no sign of urethritis, vesiculitis, cystitis, prostatitis, epididimytis, orchitis, and dysuria was reported post RISUG injection. But 41.9% subjects low to moderate grade scrotal pain was reported on 3rd day post RISUG injection which reduced significantly during subsequent follow up visits and disappeared after 2.5 month Figures 2A-2F.

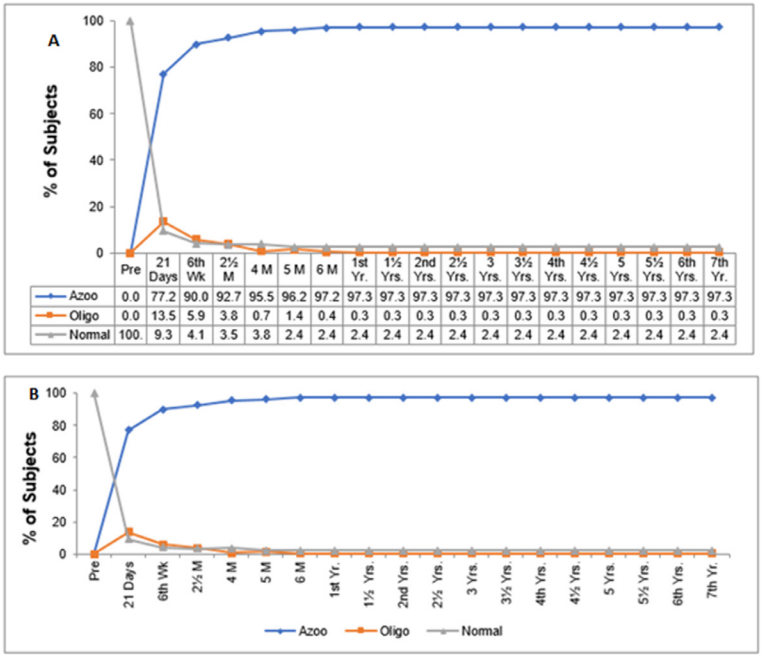

Figure 1: A) Visit-wise overall efficacy of RISUG® based on sperm count. Percent of total subjects showing azoospermia (Azoo), oligospermia (Oligo) and normospermia (Normal) over the 7-year follow-up period are shown in different colours. B) For comparison data of the visit before RISUG® injection (Pre) is also shown. **Note:** (—▲—) Azoo; (—■—) Oligo; (—×—) Normal

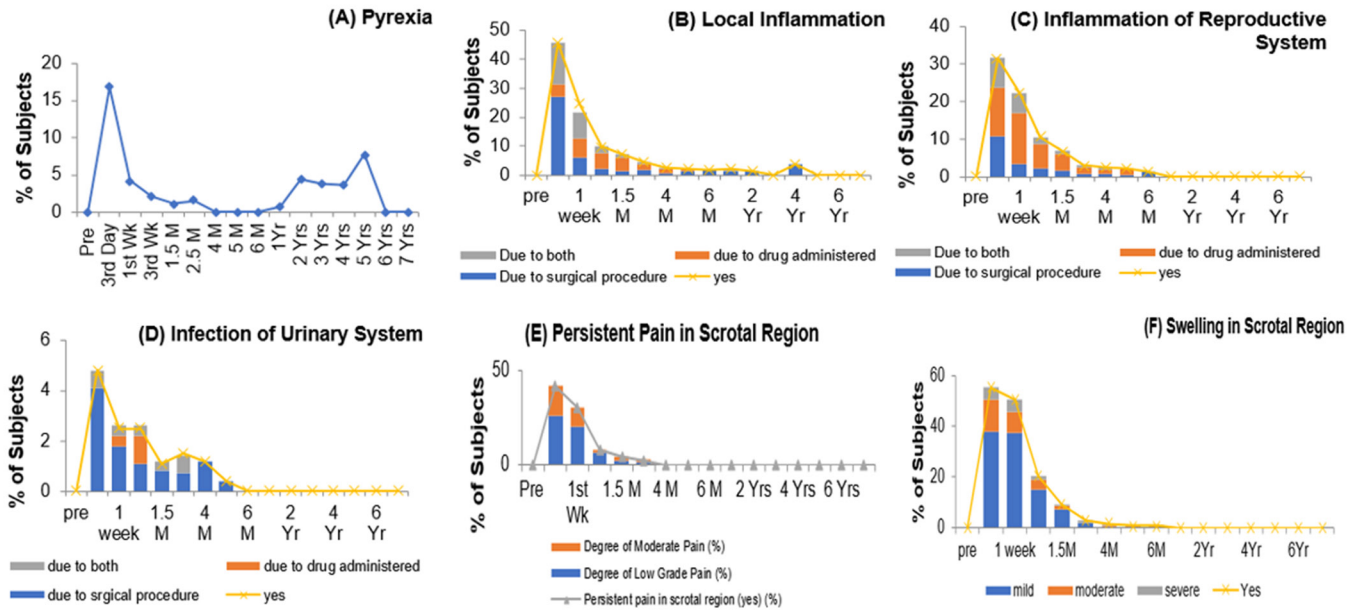

Figure 2: Visit-wise results of the clinic al examination of the male subjects after RISUG® injection. Percentage of total subjects showing (A) Pyrexia, (B) Local inflammation, (C) Inflammation of reproductive system, (D) Infection of urinary system, (E) Persistent pain in scrotal region, and (F) Swelling in scrotal region during a 7-year period after RISUG® injection. For comparison data of the visit before RISUG® injection (Pre) is also shown in each plot. Note the different Y-axis scale in each plot.

Similarly, in 55.4% subjects mild to moderate scrotal swelling was observed on 3rd day post RISUG injection which reduced significantly during subsequent follow up visits and disappeared after 2.5 month. Urethritis, epididymitis, orchitis, dysuria, scrotal lump and scrotal abscess were noticed in only 0.3%, 5.1%, 7.1%, 1%, 21.6% and 1.7% subjects respectively on the 3rd day but soon got resolved in all the subjects during subsequent visits. Scrotal nodule was noticed in 34.5% subjects on the 3rd day which increased to 36.6% after one week and then gradually reduced during the subsequent follow-up visits. None of the subjects reported vasculitis, cystitis, prostatitis, scrotal cyst or testicular atrophy.

Testes shape, size and position of all the subjects were normal after RISUG® injection and remained the same till the 7th year of follow-up.

Laboratory examination of male subjects

Variation in different parameters of haemogram and blood biochemistry examinations before and after the injection RISUG injection was not statistically significant ($p>0.05$). The Venereal Disease Research Laboratory (VDRL) test was found to be negative in all the subjects before and after the RISUG. No significant variations in different parameters of urine examinations before and after RISUG injection were observed Figures 3A-3F. No traces of albumin and sugar were found in urine before and after RISUG® injection and also during subsequent follow-up visits.

Safety evaluation of wives of RISUG injected subjects

Menstrual history and clinical examination: The difference in the usual cycle length Supplementary Figure 2A and duration of bleeding Supplementary Figure 2B before and after RISUG® injection to their husbands was not statistically significant ($P>0.05$). Urinary infection, genital disorders, dysuria, pallor and palpable nymph nodes were present in only few cases before RISUG injection which decreased to nil within next few follow-up visits. Supplementary Figures 2C-2E. No statistically significant difference ($P>0.05$) was observed in systolic and diastolic blood pressures Supplementary Figures 2F and 2G and pulse rate Supplementary Figures 2H-2J. No cases of cyanosis, abnormal skin or febrile condition were found in wives of any subject.

Cardiovascular examination: No serious cardio vascular disorder was reported in wives of RISUG injected subjects till last follow up visit. In only 9.9% women, peripheral pulse was non-palpable before RISUG® injection that decreased during subsequent follow-up visits and ultimately disappeared in all subjects Supplementary Figure 3A. While only one case reported abnormal apex beat at the time of enrolment that resolved by the next visit Supplementary Figure 3B, no cases of abnormal heart sound split, click and murmurs were present before and during the subsequent visits. This may be due to the medical care given to the female subjects.

Respiratory examination: No cases of abnormal chest movement or bilateral air entry were present before and after the injection. In a mere 0.3% subjects, adventitious sounds were present before the injection but became normal during the subsequent follow-up visit.

Abdominal examination: Abnormal abdominal shape, and palpable liver, spleen and kidney were observed before the injection in 0.3%, 3.8%, 2.9% and 2.9% subjects respectively, but they became normal during the subsequent visits. No cases of hernia were noticed both before and after the injection.

Gynecological examination: In majority of subjects, uterus position was anteverted and fornix bilateral was free and they remained the same during the sub-sequent follow-up visits Supplementary Figures 4A and 4B. Adnexa tenderness was noticed in only 0.6% subjects before RISUG® injection which disappeared at the 6 months follow-up visit Supplemental Figure 4C.

Ultrasound and X-Ray examination: In majority of the female

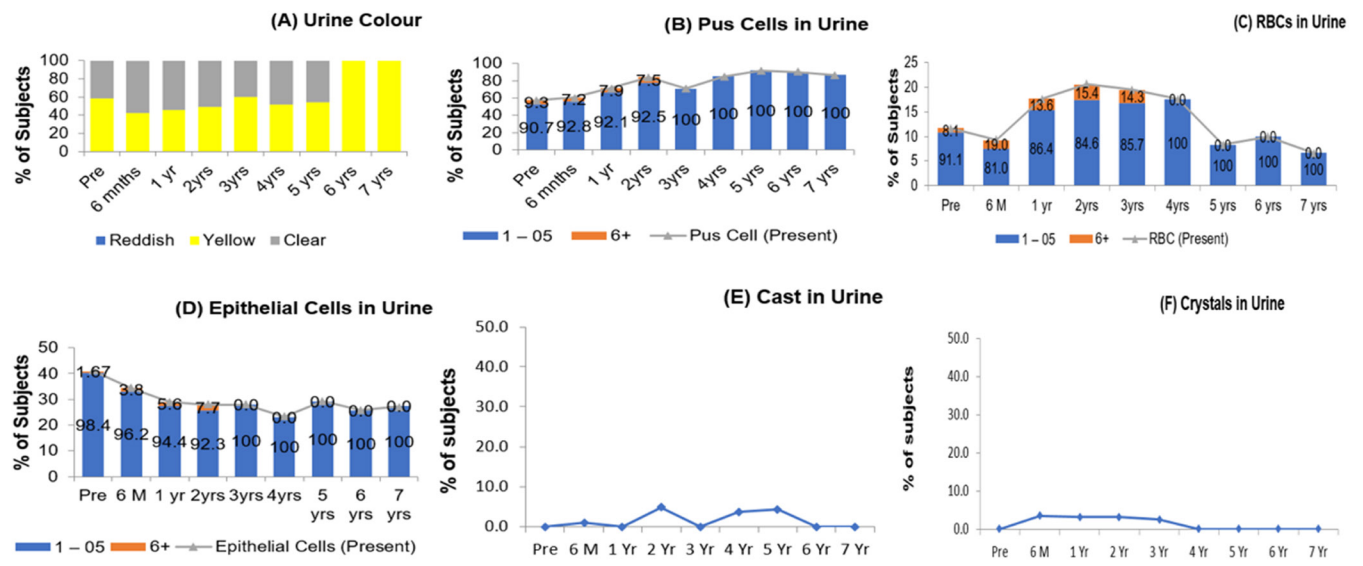

Figure 3: Visit-wise results of the urine examination of the male subjects after RISUG® injection. Percentage of total subjects showing (A) Urine colour, (B) Pus cells, (C) RBCs, (D) Epithelial cells, (E) Casts, and (F) Crystals in urine during a 7-year period after RISUG® injection. For comparison data of the visit before RISUG® injection (Pre) is also shown in each plot. Note the different Y-axis scale in each plot.

subjects, uterine sac was empty both before and after injection but in 2.8% and 2.0% subject's gestational sac was present at 6 month and 1 year follow-up visits respectively Supplementary Figure 5A. Only in few cases, ovarian cysts were noticed both at pre (3.2%) and at 6 months (2.3%) follow-up visit and became normal by at 1 year visit. However, very few new cases were observed at the 5th year (0.3%) follow-up visit which also disappeared in the subsequent visit Supplementary Figure 5B. In majority of the cases, pap smear was normal both at pre and post injection visits Supplementary Figure 5C. In few cases where inflammation and dysplasia (pap smear) and abnormal chest X-ray Supplementary Figure 5D were noticed, subjects became normal upon medical care Supplementary Figures 5C and 5D.

Haemogram and blood biochemistry: Variation in different parameters of haemogram and blood biochemistry examinations of female subjects before and after the injection is shown Supplementary Table 3. The difference in the average levels of these parameters was not statistically significant ($P>0.05$) except for blood sugar levels, before and after the injection. Results of Venereal Disease Research Laboratory (VDRL) test were found to be negative in all subjects before and after the injection.

Urine examination: Variation in different parameters of urine examination of female subjects before and after the injection is shown in Supplementary Figures 6A-6H. Only a small percentage of female subjects showed abnormal levels of these parameters but these levels reduced to zero over time.

RISUG® which is an intravasal injectable, non-hormonal, modern male contraceptive was found to be both efficacious as well as safe. The overall efficacy of RISUG® in terms of achieving azoospermia was 97.3% and based on pregnancy prevention was 99.02%. Clinical and laboratory examinations of the male subjects and their wives found no side-effects of the drug. Even if subjects showed initial complications upon RISUG® injection, they were resolved completely over the subsequent visits. Thus, RISUG® can be used as a safe male contraceptive. The advantages of RISUG® such as minimal, localized and one-time injection, long-term efficacy and negligible side-effects, make it a better choice for male contraception.

Although the Phase-III trial has been done in centres located in northern India, the cohort has subjects with heterogeneous socio-economic backgrounds from all over the India. People from all major religions and castes participated in the study indicating their acceptance of RISUG® indicating their acceptance across all the strata of society. This pan religion acceptability is probably because RISUG® method does not involve cutting and removal of any body parts.

In the history of contraceptive development, RISUG® presents the highest effectiveness compared to all other contraceptives both male and female as they were at the threshold of induction into a mass contraception program. The contraceptive action of RISUG® is due to the establishment of azoospermia as seen in 97.3% of the male subjects. This efficacy is almost similar to that observed during our earlier study [28] and reported for NSV and standard vasectomy [30]. Failure rate of RISUG® is also lower than the rate of male condom breakage that can be as high as 12.9% [29] and 18.6% [31,32]. Thus, RISUG® is a one-time male contraceptive with high efficacy and low failure rate. One important limitation with condom acceptability is the decrease in sexual pleasure. This limitation does not apply to RISUG, at least after 6 months of injection when RISUG reaches its highest efficacy levels. Beyond this point use of contraceptives such as condoms is not needed.

All male subjects showed normal baseline characteristics at the pre-injection stage. After the injection also, no serious adverse side-effects were observed during the scheduled follow-up visits up to 7 years. Complications like pyrexia, inflammation (local and reproductive system) and urinary system infection were observed in some subjects, during the visit immediately following the injection, but got completely resolved soon afterwards. Even the persistent pain and swelling in scrotal region that were reported in a many male subjects, got resolved completely within 4 months. But, the male subjects only experienced mild to moderate degree of pain and swelling. No adverse trends were observed in any parameter related to haemogram, Liver Function Test (LFT), Kidney Function Test (KFT), blood sugar, urine examination of the subjects on their scheduled follow up visits up to 7 years post RISUG® injection. Differential Leukocyte Count (DLC)-polymorphs

and serum alkaline phosphatise levels that showed significant variation before and after the RISUG® injection, were within the normal biological reference range. This shows that RISUG® does not have any long-lasting, serious adverse side-effects on male physiology.

Even though, RISUG® injection is applied to only male subjects, where the drug is localized to the vas deferens of their bodies, it was important to rule out the possibility of any inadvertent side-effect that may occur in their sexual partners. Therefore, a detailed clinical examination of all female subjects was done. Similar to their husbands, the female subjects had normal baseline characteristics at the pre-injection stage. Female subjects also, did not show any serious adverse side-effects during the scheduled follow-up visits up to 7 years post RISUG® injection to their husbands. Few subjects who displayed urinary infections, dysuria, palpable and lymph nodes etc. prior to injection were normal during subsequent visits. Similarly, even though there was a significant difference in the average levels of blood sugar levels, before and after the injection, the values were within normal biological reference range. Therefore, even the female subjects do not have any long-lasting, serious adverse side-effects due to RISUG® injection to their husbands. This means that RISUG® is not only a highly efficacious male contraceptive but also safe for both the sexual partners.

The results of the present study show that a standard dose of 120 µl of RISUG® injected into each vas deferens covers for variabilities in the lumen diameters and overall size of the vas deferens. Therefore, subject-wise dose selection need not be done. This feature helps immensely in the operation of a mass contraceptive delivery program. Findings of the study also indicate that the need for medical assistance following the RISUG® administration arises very seldom. With proper counselling at pre-injection stage and immediately after the injection, the subjects can take care of any issues that may develop on their own. Therefore, the manpower requirements in the family welfare program will not increase greatly by the introduction of RISUG®.

CONCLUSION

The data collected from all the participating centers of the Phase-III Clinical trial indicate that people from all major religion (i.e., Hindu, Muslim and Sikh) and all major caste have accepted the RISUG injection. No adverse side effect was reported and observed on clinical evaluation of these subjects even up to 7 years of post RISUG injection.

No adverse trend was observed in any parameter related to haemogram, liver function test kidney function test, blood sugar, urine examination of the subjects up to 7 years post RISUG injection. The data indicates that 92.7% subjects achieved azoospermia at 2½ month post injection and it increased 97.2% at 6th month and then reached to highest level (97.3%) during sub-sequent follow up visits post RISUG injection. The method failure rate was 1.2% with a 2.7% over all failure of the drug RISUG. Hence over all contraceptive efficacy of the drug RISUG was 97.3%. However, efficacy of drug RISUG as per preventing the pregnancy is 99.02%.

A standard dose of 120 µl of RISUG injected into each vas deferens during the trial covers for variabilities in the vas deferens lumen diameters and overall size of the vas deferens. Therefore, when in use in mass program there is the simplicity that subject wise dose selection need not be done. Findings of the study also indicate that very seldom the need for medical assistance following the RISUG administration comes up. With proper counseling pre injection and immediately after the injection the subjects can on their own take care of any issues which may come up. Therefore, the manpower requirements in the family welfare program will not be greatly increased by the introduction of RISUG.

Review of the entire phase-III clinical trial data clearly confirms that RISUG® is a safe and highly efficacious nonhormonal, once injectable male contraceptive with all the features necessary for a method to be in a mass family welfare program.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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