Clinical Study Report

Version: 1.0, Dated: 12th March 2022

"Evaluation of efficacy & safety of Isotine Eye Drops in patients suffering from immature uncomplicated cataract - An open label, comparative, Multicentric, two arm, prospective, interventional clinical study"

Protocol No. IST/01-2020 Version 1.0, 31th Oct 2020

CTRI Registration No: CTRI/2021/01/030699 [Registered on: 22/01/2021]

Sponsor

Jagat Pharma Pvt. Ltd

No- 23 B, Stadium Rd,
Model Town, Bareilly,
Uttar Pradesh 243122

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LIST OF ABBREVIATIONS:

AE/AEs- Adverse Event(s)

ANOVA- Analysis of Variance

AR/ARs- Adverse Reaction(s)

CRA- Clinical Research Associate

CRF/CRFs- Case Report Form(s)

GCP- Good Clinical Practice

GLM- General Linear Model

GLP- Good Laboratory Practice

Gm- Gram

GMP- Good Manufacturing Practice

ICF- Informed Consent Form

ICMR- Indian Council of Medical Research

IEC- Institutional Ethics committee/ Independent Ethics Committee

IP- Investigational Product

OPD- Out Subject Department

PIS- Subject Information Sheet

SAE/SAEs- Serious Adverse Event(s)

SAR/SARs- Serious Adverse Reaction(s)

WMA- World medical association

SAE- Serious Adverse Event

1. STATEMENT OF COMPLIANCE

"Evaluation of efficacy & safety of Isotine Eye Drops in patients suffering from immature uncomplicated cataract - An open label, comparative, Multicentric, two arm, prospective, interventional clinical study"

Protocol No. IST/01-2020 Version 1.0, 31th Oct 2020

We hereby certify the authenticity of the Clinical Study Report and declare that the results are an accurate interpretation of the data; to the best of our knowledge. We also hereby provide assurance that this study was conducted in compliance to the protocol and as per applicable Good Clinical Practices and Ethical Guidelines laid down by AYUSH.

Sr. No	Sponsor/CRO	Represented by	Signature & Date
1	**Sponsor** **Jagat Pharma Pvt. Ltd** No- 23 B, Stadium Rd, Model Town, Bareilly, Uttar Pradesh 243122 Ph.: +91 - Email: drmsbasu@gmail.com	Dr. Mandeep Basu	
2	**CRO** Target Institute of Medical Education and Research 402, A/B/C, Jaswanti Allied Business Center, Ramchandra lane Extension, Kachpada, Malad (West), Mumbai-400064 Email – targetinstitute@yahoo.com	Dr. Sanjay Tamoli	

Sr. No	Site	Principal Investigator / Co-Investigator	Signature & Date
1	Ayurved Seva Sanghs, Ayurved Mahavidyalaya, OPD No 7A, Ground Floor, Ayurved, Sanshodhan Vibhag, Ayurved Seva Sanghs, Ayurved Mahavidyalaya, Ganeshwadi, Panchvati, Nashik –422003	Dr Shishr Pande	
2	S.D.M. College of Ayurveda, OPD No. 7, Ground Floor, P.G. Department of Kayachikitsa and Manasaroga, S.D.M. College of Ayurveda, Kuthpady Udupi, Karnataka 574 118	Dr Sapna Bhandary	
3	Shri. Gurudeo Ayurved College, Gurukunj Ashram, Tal. Tiosa, Dist. Amravati, Pin Code - 444902	Dr. Sachin T Agiwal	

2. EXECUTIVE SUMMARY

2.1	**Protocol Title**	Evaluation of efficacy and safety of Isotine Eye Drops in patients suffering from immature uncomplicated cataract - An open label, comparative, Multicentric, two arm, prospective, interventional clinical study
2.2	**Protocol ID version & date**	Protocol No IST/01-2020 Version 1.0, 31st Oct 2020
2.3	**Study Design**	The study was an open label, comparative, Multicentric, two arm, prospective, interventional clinical study
2.4	**Duration of treatment**	Total duration of study treatment was 180 days
2.5	**Total no of visits**	Screening visit (day -3), baseline visit (day 0), Follow up visit 1 (day 30 ±5days), Follow up visit 2 (day 60 ±5days), follow up visit 3 (day 90 ±5days) and visit 4 (day 180 ±5days).
2.6	**Sample Size**	The total subjects enrolled were 69 in the study of which there were 61 completers at the end of 3 Months and 59 completers at the end of 6 Months (Evaluable cases). In Isotine group there were 30 completers at 3 months and at 6 months while in control group there were 31 completers at the end of 3 Months and 29 completers at the end of 6 Months.
2.7	**Investigational Products and Dosage**	Subjects in Isotine group were instructed to use a dose of 2 drops in each eye twice daily for a period of 6 months, while subjects in Control group were instructed to continue the conventional treatment, which they were already taking. Subjects in the Control group were not allowed to use any eye drops meant for the treatment of cataract.
2.8	**Study Objectives**	**Objective:** The objective of the study was to evaluate efficacy and safety of Isotine Eye Drop in patients suffering from immature uncomplicated Cataract by comparing against conventional management. **Primary Outcome:**

		1. Comparative assessment of changes in Lens evaluated on Lenticular Opacity Classification System II and direct and indirect ophthalmoscopy examinations between subjects using Isotine Eye Drops and those using conventional management 2. Comparative Assessment of visual acuity and quality of vision between subjects using Isotine Eye Drops and those using conventional management **Secondary Outcome:** 1. Comparative Clinical assessment of symptoms related to cataract on graded scale between subjects using Isotine Eye Drops and those using conventional management 2. Comparative Assessment of other changes in eyes related symptoms like itching, tiredness, irritation, burning etc. if any, between subjects using Isotine Eye Drops and those using conventional management 3. Global assessment for overall change by the subject at the end of 180 days of study treatment between subjects using Isotine Eye Drops and those using conventional management 4. Global assessment for overall change by the investigator at the end of 180 days between subjects using Isotine Eye Drops and those using conventional management 5. Assessment of tolerability by assessing adverse events 6. Assessment of vitals during the study period
2.9	**Tools used for Evaluation**	**Efficacy Assessment** • Visual acuity and quality of vision using Snellen's chart. • Slit lamp bio microscopic examination in tangentional sectioning of lens and retro-illumination technique for grading of cataract. **Safety Assessment** • Vital Signs • Clinical evaluation

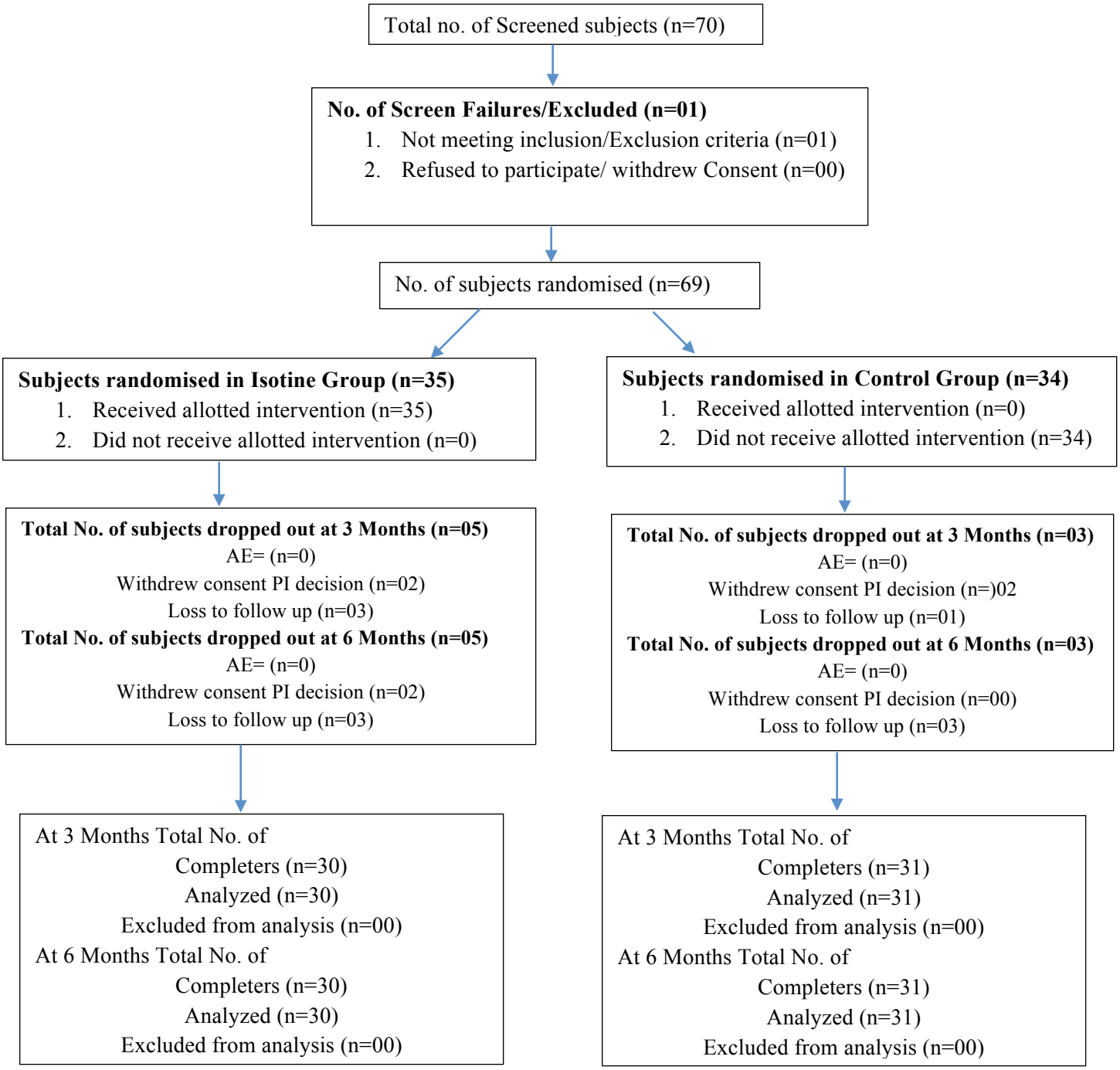
		• Concomitant, Adverse event and Serious Adverse Event Monitoring
2.10	**Inclusion Criteria**	1. Subjects of either sex in the age group of 30 to 70 years, both inclusive 2. Subjects with immature (Asymptomatic or Symptomatic) and uncomplicated cataract not requiring surgery 3. Subjects who had cataract with possible grading on slit lamp bio microscopy according to Lenticular Opacity Classification System II. 4. Subjects who were ready to provide written informed consent and who were ready to willingly participate and follow the protocol requirements of the clinical study.
2.11	**Exclusion Criteria**	1. Subjects with congenital cataract, mature and hyper mature cataract 2. Subjects who had any other ophthalmic condition like glaucoma, diabetic retinopathy, macular degeneration, retinitis pigmentosa which requires urgent and separate treatment 3. Subjects with Uncontrolled Diabetes and Uncontrolled Hypertension 4. Subjects taking Steroid treatment and or any kind of immunosuppressive therapy 5. Subjects participating in any other clinical study or have participated in any other study 3 months prior to screening in the study. 6. Subjects who were in general sensitive to any eye drops 7. A female participant who were of reproductive potential had a negative pregnancy test and agrees to use contraception throughout study period 8. Other conditions, which in the opinion of the investigators, makes the patient unsuitable for enrolment or could interfere with his participation in, and completion of the protocol
2.12	**Methodology**	The study was initiated after approval from the Institutional Ethics Committee and subsequently the study was registered with CTRI. Subjects [(male and females age between 30 – 70 years, (both inclusive)] attending OPD at site were considered for screening. On screening visit (day -3), a written informed consent was obtained from subject for his/her participation

		in the study. Subject underwent physical and systemic examinations. Subject's medical and surgical history were taken. Subject's medication if any was noted in the CRF. Subject's assessment of visual acuity and quality of vision was done using Snellen's chart. Subject's slit lamp bio microscopic examination in tangentional sectioning of lens and retro-illumination technique for grading of cataract (according to Lenticular Opacity Classification System II) and direct and indirect ophthalmoscopy examinations was done. Subject's investigations i.e. blood sugar fasting and HbA1c (only if subject had history of diabetes) and UPT (only for fertile females)] were done. Clinical symptoms if any such as blurring of vision, polyopia, nyctalopia, hamarlopia, glaring of light, colored halos, visualization of non-existing things etc. were assessed with the help of grading pattern (5=Almost always, 4=sometimes, 3= Every once in a while, 2= Rarely, 1= Never). Subject were called after three days on baseline visit (day 0). Non Diabetic subjects were recruited in the study on the same day of screening and that was considered baseline as well. On baseline visit, subjects were recruited if he/she met all the inclusion criteria. Subjects underwent general and systemic examinations. Subject's assessment of visual acuity and quality of vision were done using Snellen's chart. Clinical signs and symptoms (if any) were evaluated on subjective assessment scale. If the subjects met all the inclusion/exclusion criteria they were randomized in one of the two study arms. Subjects in one arm was given Isotine Eye Drops while subjects in the second arm were asked to continue conventional management. Subject were given study medication packed in sterile eye drops bottle. Subjects in the Study arm was asked to use Isotine eye drop in a dose of 2 drops in each eye twice daily for a period of 6 months. After

		recruitment, subjects were asked to visit site on day 30 (Visit 1), day 60 (Visit 2), day 90 (Visit 3) and day 180 (Visit 4). Subjects were allowed to come for follow up either 5 days prior or after the scheduled follow up visit, provided subject should continue the given treatment. Subjects were advised to refrain from any modern medicine, Nutraceutical, Ayurvedic, homeopathic, Siddha, Unani etc. treatment for cataract during the entire study duration. On every follow up visit, subjects underwent general and systemic examinations. Subject's assessment of visual acuity and quality of vision was done using Snellen's chart. Subject's slit lamp bio microscopic examination in tangentional sectioning of lens and retro-illumination technique for grading of cataract (according to Lenticular Opacity Classification System II) and direct and indirect ophthalmoscopy examinations was done. Clinical signs and symptoms (if any) were evaluated on subjective assessment scale. Subject's blood sugar fasting and postprandial blood sugar were checked only if subject had history of diabetes. Subjects in the study group were asked to use Isotine eye drop in a dose of 2 drops in each eye twice daily while those in the Control group were asked to continue the treatment prescribed. Compliance was assessed by asking the subjects for how many times he/she missed the dosage. Compliance of more than 80% for investigational drug was considered acceptable. On last follow up visit, tolerability of the study drug was assessed by the investigator and Subject. Global assessment for overall change was done by investigator and Subject. All the subjects were closely monitored for any adverse events/ adverse drug reactions from baseline visit till the end of the study. Subject's investigations i.e. blood sugar fasting and HbA1c only if subject has history of diabetes was done. Subjects were asked to stop trial medication and take investigator's advice for further treatment.
2.13	**Statistical**	The data were analysed for central tendencies (mean, median), range,

	method of assessment	standard error and standard deviation. Data were tabulated shown using standard format and MS Excel. Statistical tests were carried out to compare study groups as per the distribution (normality) Student's T test (normative), Mann-Whitney statistic (non-parametric), Chi-square statistic (categorical), ANOVA. The level of significance at $p < 0.05$ (two sided) was considered significant. Both intent-to-treat and per protocol completer analysis were performed when appropriate. Standard statistical software programs were used (GraphPad InStat Version 3.6).
2.14	**Results**	Details discussed in the section of Observations and Results
2.15	**Conclusion**	The present study concludes that regular use of Isotine eye drops in a dose of 2 drops twice daily for a period of 6 months helps in the management of cataract. Opthalmic assessment by Slit lamp examination and direct and indirect opthalmoscopic assessment showed improvement in the grade of cataract with the use of Isotine drops as compared to conventional management. Also the number of subjects showing improvement in their condition of cataract was found to be significantly higher with the use of Isotine Eye drops. Visual acuity was also found to be improved with the use of Isotine Eye drops. Isotine eye drops was found to be safe on regular long term use without producing any adverse effects. Further studies with larger sample size with the use of advanced testing methods for cataract assessment are required to validate the results of the study.

Subject Details (Consort)



3. ETHICS:

3.1 Ethics Committee approvals:

The study was approved by following ethics committees:

Site 01: Ayurved Seva Sanghs, Ayurved Mahavidyalaya, Nashik

Institutional Ethics Committee, Ayurved Seva Sanghs, Ayurved Mahavidyalaya, Nashik on 21/11/2020

Site 02: S.D.M. College of Ayurveda, Udupi

Institutional Ethics Committee, S.D.M. College of Ayurveda, Udupi on 04/02/2021

Site 03: Shri. Gurudeo Ayurved College, Amravati

Institutional Ethics Committee, Shri. Gurudeo Ayurved College, Amravati on 23/02/2021

3.2 Ethical conduct of the study:

The study was initiated after approval from Institutional Ethics Committees of respective sites. Study Protocol was strictly followed by all the sites. All the study related activities were conducted under the guidance of Principal Investigators or Co-investigators. All the study personals were given training in ASU-GCP guidelines for conducting the clinical study in an ethical way. The study was conducted as per approved protocol and ASU GCP guidelines.

3.3 Subject Information and Consent:

Subjects were recruited after signing the Informed Consent Document. Consent was taken after providing complete information to the subject in a written document (Subject Information Sheet). Information was given to the subjects in the language that the subjects could read and write. Subjects were given an opportunity to ask questions and their queries were resolved. In case of illiterate subjects an impartial witness was asked to sign the consent after providing complete information. All the process of Screening/Consent and recruitment were documented by the Clinical Research Coordinator in the Informed consent process document which was approved by the Principal Investigator or Co-Investigator.

4. CTRI REGISTRATIONS:

The Clinical study is registered on CTRI website with registration number CTRI/2021/01/030699 [Registered on: 22/01/2021]

5. STUDY EVENTS:

Sr. No	Event	Date
1	Study Approved by ethics committee	
	Site 01: Ayurved Seva Sanghs, Ayurved Mahavidyalaya, Nashik	21/11/2020
	Site 02: S.D.M. College of Ayurveda, Udupi	04/02/221
	Site 03: Shri. Gurudeo Ayurved College, Amravati	23/02/2021
2.	CTRI registration	22/01/2021
3.	1st Subject Enrolment date	20/02/2021
4.	Last subject Enrolment date	21/08/2021
5.	Last follow up visit of last subject	10/02/2022

6. STUDY ADMINISTRATIVE STRUCTURE AND INVESTIGATOR:

1. SPONSOR:

Jagat Pharma Pvt. Ltd
No- 23 B, Stadium Rd, Model Town, Bareilly,
Uttar Pradesh 243122

2. CRO:

Target Institute of Medical Education & Research, A wing, 402, A/B/C, Jaswanti allied business Center, Ramchandra Lane Extension, Kachpada, off link road, Malad West, Mumbai 400064

3. SITE DETAILS:

Sr. No	Site	Principal Investigator / Co-Investigator
1	Ayurved Seva Sanghs, Ayurved Mahavidyalaya, OPD No 7A, Ground Floor, Ayurved, Sanshodhan Vibhag, Ayurved Seva Sanghs, Ayurved Mahavidyalaya, Ganeshwadi, Panchvati, Nashik –422003	Dr Shishr Pande
2	S.D.M. College of Ayurveda, OPD No. 7, Ground Floor, P.G. Department of Kayachikitsa and Manasaroga, S.D.M. College of Ayurveda, Kuthpady Udupi, Karnataka 574 118	Dr Sapna Bhandary
3	Shri. Gurudeo Ayurved College, Gurukunj Ashram, Tal. Tiosa, Dist. Amravati, Pin Code - 444902	Dr. Sachin T Agiwal

7. STUDY INTRODUCTION:

A cataract is a lens abnormality characterized by decreased transparency and increased cloudiness. Cataract is the leading cause of reversible visual impairment and blindness globally. The condition is most prevalent in populations with lower socioeconomic status and developing countries. Crystallins are the main proteins making up the lens and the lens surfaces, and are responsible for their refractive function. Modification, aggregation and precipitation of crystallins are the main mechanisms underlying cataract development. Most cataracts are caused by age-related degeneration; however, cataract can also develop secondary to trauma or as a consequence of another disease. Cataract rarely occurs in children. The symptoms of cataract include blurry vision, trouble seeing at night, seeing colors as faded, increased sensitivity to glare, halos surrounding lights, double vision in the affected eye, a need for frequent changes in prescription glasses.[1] Linganasha mentioned in Ayurvedic literature can be correlated to modern day cataract. Linganash means loss of vision (Dalhan). Two varieties of Linganasha have been described i.e. reversible and irreversible or curable and incurable.[2, 3]

The only treatment for cataract is surgery. Phacoemulsification is the gold standard for cataract surgery in the developed world, whereas manual small incision cataract surgery is used frequently in developing countries. In general, the outcomes of surgery are good and complications, such as endophthalmitis, often can be prevented if properly managed. Femtosecond laser-assisted cataract surgery, an advanced technology, can automate several steps; initial data show no superiority of this approach over current techniques, but the results of many large clinical trials are pending. The greatest challenge remains the growing 'backlog' of patients with cataract blindness in the developing world because of lack of access to affordable surgery. In the absence of strategies that can prevent or delay cataract formation, it is important to focus efforts and resources on developing models for efficient treatment of cataract. [1]

Jagat Pharma Pvt. Ltd. has developed an eye drop i.e. Isotine Eye drop for the treatment of cataract. It contains Splash, Apamrg, Punarnava, Yashed Bhasma, Tankana bhasma, alum, Tuth Bhasma, Satva Purina, benzalkonium. The ingredients present in the Isotine eye drop help improve vision and delays progression of cataract. To test this hypothesis a clinical study titled "Evaluation of efficacy and safety of Isotine Eye Drops in patients suffering from immature uncomplicated cataract - An open label, comparative, Multicentric, two arm, prospective, interventional clinical study" was conducted.

8. STUDY OBJECTIVES AND PURPOSE:

The Objectives of the study was to evaluate efficacy and safety of Isotine Eye Drop in patients suffering from immature uncomplicated Cataract by comparing against conventional management.

8.1 Primary Objectives:

1) Comparative assessment of changes in Lens evaluated on Lenticular Opacity Classification System II and direct and indirect ophthalmoscopy examinations between subjects using Isotine Eye Drops and those using conventional management
2) Comparative assessment of changes in visual acuity and quality of vision between subjects using Isotine Eye Drops and those using conventional management

8.2 Secondary Objectives:

1) Comparative assessment of changes in clinical symptoms related to cataract between subjects using Isotine Eye Drops and those using conventional management
2) Comparative assessment of changes in other symptoms like tiredness, itching, irritation etc. if any between subjects using Isotine Eye Drops and those using conventional management
3) Global assessment for overall change by the subject at the end of 180 days of study treatment
4) Global assessment for overall change by the investigator at the end of 180 days
5) Assessment of tolerability of study drug by assessing adverse events and serious adverse events during the study period.
6) Assessment of vitals during the study period

9. TEST PRODUCT DETAILS:

9.1 Product Name: Isotine Eye Drops

9.2 Ingredients: Each capsule contains: Splash, apamrg, punarnava, yashed Bhasin, tankana bhasma, alum, tuth Bhasma, Satva Purina, benzalkonium

9.3 Dosage form: 2 drops in each eye twice daily for a period of 6 months.

10. STUDY METHODOLOGY:

10.1 Study design and Duration:

The study was an Open label, Comparative, two arm, Multicentric, interventional, prospective, clinical study.

10.2 Assessment of Efficacy end points:

10.2.1 Primary efficacy and safety end point:

1. Comparative assessment of changes in Lens evaluated on Lenticular Opacity Classification System II and direct and indirect ophthalmoscopy examinations between subjects using Isotine Eye Drops and those using conventional management
2. Comparative assessment of changes in visual acuity and quality of vision between subjects using Isotine Eye Drops and those using conventional management

10.2.2 Secondary efficacy and safety end point:

1. Comparative assessment of changes in clinical symptoms related to cataract between subjects using Isotine Eye Drops and those using conventional management
2. Comparative assessment of changes in other symptoms like tiredness, itching, irritation etc. if any between subjects using Isotine Eye Drops and those using conventional management
3. Global assessment for overall change by the subject at the end of 180 days of study treatment
4. Global assessment for overall change by the investigator at the end of 180 days
5. Assessment of tolerability of study drug by assessing adverse events and serious adverse events during the study period.
6. Assessment of vitals during the study period

10.3. Inclusion Criteria:

1) Subjects of either sex in the age group of 30 to 70 years, both inclusive
2) Subjects with immature (Asymptomatic or Symptomatic) and uncomplicated cataract not requiring surgery
3) Subjects who had cataract with possible grading on slit lamp bio microscopy according to Lenticular Opacity Classification System II.

4) Subjects who were ready to provide written informed consent and who were ready to willingly participate and follow the protocol requirements of the clinical study**.**

10.4 Exclusion Criteria:

1) Subjects with congenital cataract, mature and hyper mature cataract
2) Subjects who had any other ophthalmic condition like glaucoma, diabetic retinopathy, macular degeneration, retinitis pigmentosa which requires urgent and separate treatment
3) Subjects with Uncontrolled Diabetes and Uncontrolled Hypertension
4) Subjects taking Steroid treatment and or any kind of immunosuppressive therapy
5) Subjects participating in any other clinical study or have participated in any other study 3 months prior to screening in the present study.
6) Subjects who were in general sensitive to any eye drops
7) A female participant who were of reproductive potential had a negative pregnancy test and agrees to use contraception throughout study period
8) Other conditions, which in the opinion of the investigators, makes the patient unsuitable for enrolment or could interfere with his participation in, and completion of the protocol.

11. ASSESSMENT PARAMETERS:

11.1Assessment of Efficacy Parameter:

The study involved the use of slit lamp bio microscopic examination in tangential sectioning of lens and retro-illumination technique for grading of cataract and also various scales for overall change and safety. The investigator assisted /explained /guided/helped the subject in filling up the scores in these scales wherever required.

11.1.1 Assessment of changes in Lens evaluated on Lenticular Opacity Classification System II and direct and indirect ophthalmoscopy examinations:

Ophthalmologist had evaluated lens at the baseline visit and thereafter at all follow up visits on direct and indirect ophthalmoscopy and evaluate on lenticular classification system II. Comparative assessment for changes in the lens was done both within the group (baseline to 90 days and 180 days) and also between the two groups.

11.1.2 Assessment of visual acuity and quality of vision:

Visual acuity was checked on baseline visit and thereafter at follow up visits on Snelle's chart. Comparative assessment for changes in the visual acuity and quality of vision was done both within the group (baseline to 90 days and 180 days) and also between the two groups.

11.1.3 Clinical assessment of symptoms related to cataract:

Clinical symptoms like blurring of vision, polyopia, nyctalopia, hamarlopia, glaring of light, colored halos, visualization of non-existing things etc. were assessed with the help of grading pattern (5=Almost always, 4=sometimes, 3= Every once in a while, 2= Rarely, 1= Never) at baseline visit and thereafter at follow up visits. Comparative assessment for changes in the clinical symptoms was done both within the group (baseline to 90 days and 180 days) and also between the two groups.

11.1.4 Assessment of other symptoms related to Eyes:

Other symptoms like irritation, dryness, tiredness, burning were evaluated on a scale of (No-0, Mild -1, Moderate-2, severe 3) at baseline and thereafter at all follow up visits. Comparative assessment for changes in the symptoms were done both within the group (baseline to 90 days and 180 days) and also between the two groups.

11.1.5 Global assessment for overall change by the subject and by Investigator at the end of 180 days of study treatment:

This was assessed with regards to the overall change based on the clinical symptoms and ophthalmic examination as per the investigator on the following parameters:

0 = No Change	4 = Slight worsening from baseline
1 = Slight Improvement as compared to baseline	5 = Moderate worsening from baseline
2 = Marked or moderate improvement from baseline	6 = Significant worsening from baseline
3 = Excellent or significant improvement from baseline	

11.2 Assessment of Safety

Safety was assessed by clinical review of all safety parameters, including the following:

a. Adverse event reporting, as applicable

b. Vital signs including allergic reactions etc.

c. Assessment of Overall Safety and Tolerability of the study drug by the physician and subject on global assessment scale by the investigator and by subject himself. The criterion for the global

assessment of overall safety was as follows:

1= Excellent Overall safety (No adverse event/s reported)

2= Good Overall safety (Mild adverse events (s) reported which subside with or without medication)

3= Fair Overall safety (Moderate to severe adverse event(s) reported which subside with or without medication and do not necessitate stoppage of study treatment)

4= Poor Overall safety (Severe or serious adverse event(s) which necessitate stoppage of study.)

Safety variables were listed individually for detailed clinical review, when needed. Additional tables summarized adverse events by severity and relationship to study product as well as leading to SAEs and withdrawal of the subjects from the trial.

Appendix I: Table of Assessment

Activity	Screening Visit (Day -3)	Baseline Visit (Day 0)	Visit 1 (Day 30) ±5 days	Visit 2 (Day 60) ±5 days	Visit 3 (Day 90) ± 5 days	Visit 4 (Day 180) ± 5 days
Assessment of Inclusion/ Exclusion Criteria	√	√	X	X	X	X
Written Informed Consent	√	X	X	X	X	X
Demographic Data and History	√	X	X	X	X	X
Physical and systemic Examinations	√	√	√	√	√	√
Subject's assessment of visual acuity and quality of vision using Snellen's chart.	√	√	√	√	√	√
Slit lamp bio microscopic examination in tangentional sectioning of lens and retro-illumination technique for grading of cataract	√	√	√	√	√	√
Assessment of Signs and Clinical Symptoms	√	√	√	√	√	√
Fasting and HbA1c only if subject is suffering from diabetes	√	X	√	√	√	√
UPT (only for fertile females)	√	X	X	X	X	√
Drug Dispensing	X	√	√	√	√	X
Global assessment of overall change by investigator and by Subject	X	X	X	X	X	√
Global assessment of tolerability of trial drug by investigator and by Subject	X	X	X	X	X	√
Assessment of vitals, safety and ADR/Adverse Events monitoring	√	√	√	√	√	√
Drug Compliance	X	X	√	√	√	√

12. STUDY VISIT DETAILS:

12.1. Study population and pre study screening evaluation

Written informed consent was obtained from the Subject prior to screening for possible inclusion in the study. During Informed consent process, they were given enough time to read the Informed Consent Form (ICF) & Subject Information Sheet (SIS) which was printed in the languages best understood by them. Subjects were given freedom to ask the questions and all questions were answered by the Investigator or by other study staff. Subjects who agreed to participate in the study, a written informed consent for the same was obtained from him/her.

The screening phase was designed to confirm that the subject fulfilled all inclusion and exclusion criteria. The baseline evaluations were completed prior to the initiation of study treatments.

A screening log was maintained at the site where all subjects screened for possible inclusion were enlisted, irrespective of whether or not the subjects are finally enrolled into the study. Those who do not fulfilled the inclusion/exclusion criteria was recorded as 'screening failures'.

The following activities were performed at Screening Visit:

- Subjects were screened for eligibility criteria.
- On screening visit, a written informed consent was obtained from subjects for their participation in the study.
- Subject's blood sample was collected at the respective study centers for lab tests i.e. blood sugar fasting and postprandial blood sugar only if subject had history of diabetes and UPT (only for fertile females)] was done
- Demographic details were recorded. General Physical and clinical examination were done.
- Subject's assessment of visual acuity and quality of vision were done using Snellen's chart.
- Subject's slit lamp bio microscopic examination in tangentional sectioning of lens and retro-illumination technique for grading of cataract (according to Lenticular Opacity Classification System II) and direct and indirect ophthalmoscopy examinations was done.
- Clinical symptoms if any such as blurring of vision, polyopia, nyctalopia, hamarlopia, glaring of light, colored halos, visualization of non-existing things etc. were assessed with the help of grading pattern (5=Almost always, 4=sometimes, 3= Every once in a while, 2= Rarely, 1=

Never).

- Subjects were advised to continue their usual routine diet and exercise/activity regimen, which they were already following, during the entire study period. Subjects was advised to come to hospital/site for baseline visit within three days after screening visit.

12.2. Procedures performed during the study period

A) Baseline Visit (Day 0):

- Subjects who met the inclusion/exclusion criteria were randomized to one of the two study groups. Randomization was done on the basis of computer generated randomization list.
- Subject were asked for any AE/SAE occurred during last 3 days. If subject had AE/SAE, the details of the incidence were documented in the source document and CRF.
- Subjects underwent general and systemic examinations.
- Subject's assessment of visual acuity and quality of vision were done using Snellen's chart. Clinical signs and symptoms (if any) was evaluated on subjective assessment scale.
- Subject were given study medication packed in sterile eye drops bottle. Subjects was asked to use Isotine eye drop in a dose of 2 drops in each eye twice daily for a period of 6 months. Subjects were allowed to come for follow up either 5 days prior or after the scheduled follow up visit, provided subject had continued the given treatment.
- Subject were asked for any AE/SAE occurred. If subject had AE/SAE, the details of the incidence were documented in the source document and CRF. SAE, if any, was reported to the IEC in a SAE reporting form. Rescue medication used, if any, were recorded in the CRF. Subject was then asked to come for subsequent follow ups on day 30, day 60 and day 90 and day 180.

B). Follow up Visits: Visit 1 (Day 30 + 5 days), Visit 2 (Day 60 + 5 days), Viist 3 (Day 90 ± 5 days):

- On every follow up visit, subjects underwent general and systemic examinations.
- Subject's assessment of visual acuity and quality of vision were done using Snellen's chart.
- Subject's slit lamp bio microscopic examination in tangentional sectioning of lens and retro-illumination technique for grading of cataract (according to Lenticular Opacity Classification System II) and direct and indirect ophthalmoscopy examinations were done.
- Clinical signs and symptoms (if any) was evaluated on subjective assessment scale.

- Subject's blood sugar fasting and postprandial blood sugar were checked only if subject had history of diabetes.
- Subject were given study medication packed in HDPE bottle. Subjects were asked to use Isotine eye drop in a dose of 2 drops in each eye twice daily.
- Compliance were assessed by asking the subjects for how many times he/she missed the dosage.
- Compliance of more than 80% for investigational drug were considered acceptable.

C). Visit 3 - End of Study (Day 180+ 5 days):

- On last follow up visit, tolerability of the study drug was assessed by the investigator and patient.
- Subject's investigations i.e. blood sugar fasting and postprandial blood sugar only if subject has history of diabetes and UPT (only for fertile females)] were done.
- The bottle provided to the subject on the previous visit was collected.
- Subject's global evaluation for overall change and Investigator's global evaluation for overall change were done on completion of the study.
- Subjects were asked for any adverse event during this period. If subject had AE/SAE, the details of the incidence were documented in the source document and CRF. SAE, if any, was reported to the IEC in a SAE reporting form. Rescue medication used, if any, were recorded in the CRF.
- After completion of 180 days of study treatment, Subjects were advised to stop trial medication & take advice of investigator for further treatment. All the subjects were asked to take advice of investigator for further treatment.

13. STUDY POPULATION

A total of 70 subjects were screened of which 69 subjects were randomised in the study. A total of 61 subjects were considered as completers for 3 months, a total of 59 subjects were considered as completers for 6 months (Evaluable cases). Out of these 69 subjects, 35 subjects were in Isotine Group and 34 subjects were in Control Group. All the subjects who took at least one dose of the study drug and who gave at least one post baseline efficacy measurement were considered for safety evaluation in the study. All cases that completed the study as per the protocol were considered as "Per Protocol Population". Also all cases who took at least one dose of the study drug were considered as "Safety population" and were evaluated.

14. OBSERVATIONS AND RESULTS

In the present study, a total of 70 subjects were screened. There was 01 Screen failure, as the subject did not meet the inclusion/exclusion criteria from the study. Out of the 69 subjects who were randomized, there were 35 subjects in Isotine Group and 34 subjects in Control Group. A total of 8 Subjects dropped out from study, 5 subjects in Isotine Group and 3 subjects in Control Group. Out of 5 drop outs in Isotine group, 2 dropped out due to withdrawal of the consent/PI decision while 3 dropped out due to loss to follow up. Out of 3 drop outs in Control group, all 3 dropped out due to lost to follow up. None of the subject dropped out from the study due to occurrence of adverse events. All the subjects who took even a single dose of the study drug were considered for safety evaluation.

14.1 Demographic details:

14.1.1 Baseline Demography:

The average age of subjects in Isotine group was 56.20±8.04 while in the Control group it was 55.23±7.94. There were 16 Female and 14 males in the Isotine group while the respective number were 15 and 16 in the Control group. The mean weight and BMI of the subjects in Isotine group was 62.80±13.61 kg and 24.59 ±3.99 Kg/m^2 respectively while that in Control group was 62.96 ±10.77 kg and 24.85 ±3.36 Kg/m^2 respectively. The mean BSL Fasting of the subjects in Isotine Group was 112.3±53.46 mg/dL while in the Control Group it was 97.55 ±42.75 mg/dL. 1 subject had Type II DM in Isotine group while 3 subjects had it in Control group. 4 subjects had Hypertension in Isotine Group while 5 subjecs had it in Control Group. 3 subjects had Type II DM along with Hypertension in both Isotine and Control groups. There were no subjects with Hyperthyroidism in the Isotine Group while one subject had it in Control group. The details are presented in table 1.

Table 1: Baseline Demography in the two study groups

		Isotine Group (N=30)	Control Group (N=31)	P-Value
Age in Years		56.20 ±8.04	55.23 ±7.94	0.6358
Gender	**Male**	14 (46.66%)	16 (51.61%)	p>0.05
	Female	16 (53.33%)	1548.38%	
Weight in Kgs		62.80 ±13.61	62.96 ±10.77	0.9600
BMI in Kgs/m^2		24.59 ±3.99	24.85 ±3.36	0.7877
DM		1 (3.33%)	3 (9.67%)	p>0.05
Hypertension		4 (12.90%)	5 (16.12%)	p>0.05
DM + Hypertension		3 (10%)	3 (9.67%)	p>0.05
Hyperthyroid		0	1 (3.22%)	p>0.05
BSL Fasting (mg/dL)		112.3 ±53.46	97.55 ±42.75	0.3100

14.1.2 Prakruti wise distribution of subjects:

In Isotine group, 1 (3.33%) subject had Vataj prakruti, 2 (6.67%) subjects had Vata Pittaj prakruti, 6 (20.00%) subjects had Pittaj prakruti, 3 (10.00%) subjects had Pitta Vataja prakruti, 9 (30.00%) subjects had Pitta Kaphaj prakruti, 3 (10.00%) subjects had Kaphaj prakruti, 4 (13.33%) subjects had Kapha Pittaja prakruti, and 2 (6.67%) subjects had Vata Pittaj prakruti.

In Control group, 2 (6.45%) subjects had Vataj prakruti, 2 (6.45%) subjects had Vata Pittaj prakruti, 2 (6.45%) subjects had Tridoshaj prakruti, 6 (19.36%) subjects had Pittaj prakruti, 4 (12.91%) subjects had Pitta Vataja prakruti, 6 (19.35%) subjects had Pitta Kaphaj prakruti, 4 (12.90%) subjects had Kaphaj prakruti, 2 (6.45%) subjects had Kapha Vataj prakruti, and 3 (9.68%) subjects had Kapha Pittaja prakruti. The details are presented in table 2.

Table 2: Prakruti wise distribution of subjects in two groups

	Isotine Group	Control Group
Vataj	1 (3.33%)	2 (6.45%)
Vata Pittaj	2 (6.67%)	2 (6.45%)
Tridoshaj	0 (0.00%)	2 (6.45%)
Pittaj	6 (20.00%)	6 (19.36%)
Pitta Vataja	3 (10.00%)	4 (12.91%)
Pitta Kaphaj	9 (30.00%)	6 (19.35%)
Kaphaj	3 (10.00%)	4 (12.90%)
Kapha Vataj	0 (0.00%)	2 (6.45%)
Kapha Pittaja	4 (13.33%)	3 (9.68%)
Vata Pittaj	2 (6.67%)	0 (0.00%)
Total	30 (100%)	31 (100%)

14.2 Primary Outcomes:

14.2.1 Comparative assessment of changes in Lens evaluated on direct and indirect ophthalmoscopy examinations and Lenticular Opacity Classification System II (Slit Lamp evaluation)

A) Assessment of changes in direct and indirect ophthalmoscopy examinations

Of the 30 subjects in Isotine group 3 subjects (10%) showed improvement on opthalmic assessment at the end of 3 months while 27 (90%) subjects did not show any change in this period. At the end of 6 months 9 subjects (30%) showed improvement while 21 (70%) subjects showed no change in Isotine group. None of the subjects showed worsening of cataract in this group.

In the conventional treatment group, of the 31 subjects, 29 subjects (93.54%) showed no change, 1 subject (3.22%) showed improvement while 1 subject (3.22%) showed worsening at the end of 3 months. At the end of 6 months 26 subjects (83.70%) showed no change while 1 subject (3.22%) showed improvement. 4 subjects (12.90%) showed worsening at the end of 6 months in this group.

Assessment between the groups, showed that a statistically significant higher number of subjects showed improvement in Isotine group as compared to the conventional treatment group. Details shown in table 3.

Table 3: Changes in Ophthalmoscopy examination

Parameter	**Isotine Group**		**Control Group**	
	BV to 3 Months (N=30)	**BV to 6 Months (N=30)**	**BV to 3 Months (N=31)**	**BV to 6 Months (N=31)**
No Change	27 (90%)	21 (70%)	29 (93.54%)	26 (83.70%)
Worsening	0	0	1 (3.22%)	4 (12.90%)
Improvement	3 (10%)	9 (30%)	1 (3.22%)	1 (3.22%)
P Value (BV- 3 Months)				0.357795
P Value (BV- 6 Months)				0.004257

B) Assessment of changes in Gradation of direct and indirect ophthalmoscopy examinations:

At baseline visit 21 subjects had grade I cataract in each of the two groups while 9 subjects in Isotine group and 10 subjects in control group had grade II cataract. At the end of 3 months of study 24 subjects (80%) in Isotine group had Grade I while 6 subjects (20%) had grade II cataract. At the end of 6 months of the study none of the subjects had grade Ii cataract while all 30 subjects had grade 1 cataract. In the control group 22 subjects (70.96%) had grade I while 9 subjects (29.03%) had grade II cataract at the end of 3 months. The number of subjects having grade I cataract reduced to 18 (58.06%) at the end of 6 months while those having grade II and grade III cataract increased to 11 subjects (35.48%) and 2 subjects (6.45%) respectively. Analysis between the groups showed that there was a significant improvement in cataract grade in subjects using Isotine group while those in the control group showed worsening of their condition.

Table 4: Changes in Gradation of Ophthalmoscopy:

Gradation	Isotine Group			Control Group		
	BV (n=30)	3 Months (n=30)	6 Months (n=30)	BV (n=31)	3 Months (n=31)	6 Months (n=31)
Grade I	21 (70.00%)	24 (80.00%)	30 (100%)	21 (67.74%)	22 (70.96%)	18 (58.06%)
Grade II	9 (30.00%)	6 (20.00%)	0 (0.00%)	10 (32.26%)	9 (29.03%)	11 (35.48%)
Grade III	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (00.00%)	2 (6.45%)
P value between the groups				0.371093	0.412793	0.000337

C. Assessment of changes in Lens evaluated on Lenticular Opacity Classification System II (Slit Lamp examination)

On slit lamp examination of cataract it was observed that a total of 3 subjects (10%) showed improvement while 2 subjects (6.66%) showed worsening of cataract and 25 subjects (83.33%) showed no change at the end of 3 months in Isotine group. At the end of 6 months of the study 9 subjects (30%) showed improvement while 2 subjects (6.66%) showed worsening and the remaining 19 subjects (63.33%) showed no change in their cataract condition in this group.

In the control group, on slit lamp assessment it was observed that of the 31 subjects, 28 subjects (90.32%) showed no change while 1 subject showed improvement and 2 subjects (6.45%) showed

worsening at the end of 3 months. Further at the end of 6 months 26 subjects (83.87%) showed no change while 4 subjects (12.90%) showed worsening and 1 subject (3.22%) showed improvement in their cataract condition.

On analysis between the groups it was observed that there was a significant improvement recorded in subjects using Isotine eye drops as compared to control. Details shown in table 5.

Table 5: Assessment of Changes in the Slit Lamp examination

Parameter	**Isotine Group (N=30)**		**Control Group**	
	BV to 3 Months	**BV to 6 Months**	**BV to 3 Months (N=31)**	**BV to 6 Months (N=29)**
No Change	25 (83.33%)	19 (63.33%)	28 (90.32%)	26 (83.87%)
Worsening	2 (6.66%)	2 (6.66%)	2 (6.45%)	4 (12.90%)
Improvement	3 (10%)	9 (30%)	1 (3.22%)	1 (3.22%)
P Value (BV- 3 Months)				0.561657
P Value (BV- 6 Months)				0.022001

D. Assessment of changes in Gradation of Lens evaluated on Lenticular Opacity Classification System II (Slit Lamp examination)

At baseline visit 18 subjects had grade I cataract in Isotine group while in control group it was observed in 23 subjects. 8 subjects in Isotine group and 5 subjects in control group had grade II cataract while 4 subjects had grade III cataract in Isotine group and 3 subjects had grade III cataract in control group. At the end of 3 months of the study 24 subjects (80%) in Isotine group had Grade I, 4 subjects (13.33%) had grade II cataract while 2 subjects had grade III cataract. At the end of 6 months of the study none of the subjects had grade III cataract while all 28 subjects had grade 1 cataract and 2 subjects (6.66%) had grade II cataract. In the control group 24 subjects (77.42%) had grade I while 4 subjects (12.90%) had grade II cataract and 3 subjects (9.68%) had grade III cataract at the end of 3 months. The number of subjects having grade I cataract reduced to 19 (61.29%) at the end of 6 months while those having grade II and grade III cataract increased to 7 subjects (22.58%) and 5 subjects (16.12%) respectively. Analysis between the groups showed that there was a significant improvement in cataract grade in subjects using Isotine group while those in the control group showed worsening of their condition.

Table 6: Changes in Gradation of Slit Lamp Bio

Gradation	Isotine Group (N=30)			Control Group (N=31)		
	BV	3 Months	6 Months	BV	3 Months	6 Months
Grade I	18 (60.00%)	24 (80.00%)	28 (93.33%)	23 (74.19%)	24 (77.42%)	19 (61.29%)
Grade II	8 (26.67%)	4 (13.33%)	2 (6.66%)	5 (16.13%)	4 (12.90%)	7 (22.58%)
Grade III	4 (13.33%)	2 (6.66%)	0 (0.00%)	3 (09.68%)	3 (09.68%)	5 (16.12%)
P value between groups				0.489458	0.912262	0.008707

14.2.2 Comparative Assessment of visual acuity and quality of vision

Of the 30 subjects in Isotine group 4 subjects (13.33%) showed improvement in their visual acuity at the end of 3 months while 22 (73.33%) subjects did not show any change in this period and 4 subjects showed worsening of visual acuity. At the end of 6 months 9 subjects (30%) showed improvement while 19 subjects (63.33%) subjects showed no change in Isotine group and 2 subjects showed worsening of visual acuity. In the control group, of the 31 subjects, 28 subjects (%) showed no change, 1 subject (%) showed improvement while 2 subjects (6.45%) showed worsening at the end of 3 months. At the end of 6 months 26 subjects (83.87%) showed no change while 1 subject (3.22%) showed improvement. 4 subjects (12.90%) showed worsening at the end of 6 months in this group.

Assessment between the groups, showed that a statistically significant higher number of subjects showed improvement in Isotine group as compared to the conventional treatment group.

Table 7: Assessment of Changes in Visual Acuity and Quality of vision

Parameter	Isotine Group (N=30)		Control Group (N=31)	
	BV to 3 Months	BV to 6 Months	BV to 3 Months	BV to 6 Months
No Change	22 (73.33%)	19 (63.33%)	28 (90.32%)	26 (83.87%)
Worsening	4 (13.33%)	2 (6.66%)	2 (6.45%)	4 (12.90%)
Improvement	4 (13.33%)	9 (30%)	1 (3.22%)	1 (3.22%)
P Value (BV- 3 Months)				0.204832
P Value (BV- 6 Months)				0.017066

14.3 Secondary Outcomes:

14.3.1 Comparative Clinical assessment of symptoms related to cataract on graded scale:

In Isotine Group, the mean Blurring of Vision at Baseline visit was 4.23 ±1.22, which reduced to 3.93±1.25 at 3 Month Visit and further significantly reduced to 2.86 ±1.55 at the end of the study. At Baseline visit, the mean Blurring of Vision in Control group was 3.80 ±1.30, which reduced to 3.56 ±1.43 at the end of 3 months and further significantly reduced to 3.29 ±1.57 at end of the study. When compared between the groups, the difference was found to be statistically non-significant.

In Isotine Group, the mean Polyopia at baseline visit was 1.40 ±0.85, which showed no change at the end of 3 months while it reduced to 1.27 ±0.70 at the end of the study. At baseline visit, the mean Polyopia in Control group was 1.22 ±0.76, which reduced to 1.16 ±0.79 at the end of 3 months and increased to 1.20 ±0.86 at end of the study. When compared between the groups, the difference was fount to be statistically non-significant.

In Isotine Group, the mean Nyctalopia at baseline visit was 1.80 ±1.37, which reduced to 1.50 ±1.16 and 1.39 ±1.06 at the end of 3 months and 6 months respectively. At baseline visit, the mean Nyctalopia in Control group was 1.51 ±1.06, which reduced to 1.50 ±0.97 and 1.41±0.95 at the end of 3 months visit and at end of the study. When compared between the groups, the difference was found to be statistically non-significant.

In Isotine Group, the mean Hamarlopia score at baseline visit was 1.63 ±1.24, which reduced to 1.40 ±0.93 and 1.20 ±0.49 at the end of 3 months and at the end of the study respectively. At Baseline visit, the mean Hamarlopia score in Control group was 1.23 ±0.61, which showed slight change to 1.13 ±0.62 at the end of 3 months 6 months. When compared between the groups, the difference was found to be statistically non-significant.

In Isotine Group, the mean Glaring of light at baseline visit was 2.00 ±1.41, which increased to 2.16 ±1.36 at the end of 3 months and reduced to 1.62 ±1.01 at the end of the study. At baseline visit, the mean Glaring of light in Control group was 2.23 ±1.45, which reduced to 2.17 ±1.44 and 2.16 ±1.42 at the end of 3 months and 6 months respectively. When compared between the groups, the difference was fount to be statistically Non-significant.

In Isotine Group, the mean Colored halos score at baseline visit was 1.10 ±0.40, which increased to 1.16±0.37 at the end of 3 monthswas recorded back as 1.10 ±0.30 at the end of the study. At Baseline visit, the mean Colored halos score in Control group was 1.06 ±0.35, which increased to 1.10±0.48 at the end of 3 and 6 months. When compared between the groups, the difference was found to be statistically Non-significant.

In Isotine Group, the mean Visualization of Non-existing things at baseline visit was 1 ±0, which showed no change at the end of 3 months and increased slightly to 1.03 ±0.18 at the end of the study. At baseline visit, the mean Visualization of Non-existing things in Control group was 1.00 ±0, which showed no change at the end of 3 months and 6 months. When compared between the groups, the difference was found to be statistically non-significant. The details are presented in table 8.

Table 8: Assessment of symptoms related to cataract

		Isotine Group (N=30)	Control Group (N=31)	P-Value
Blurring of Vision	**BV**	4.23 ±1.22	3.806 ±1.302	0.1370
	3 Months	3.933 ±1.258	3.567 ±1.431	0.2995
	6 Months	2.86 ±1.55**	3.290 ±1.575*	0.2682
Polyopia	**BV**	1.40 ±0.85	1.22 ±0.76	0.2817
	3 Months	1.40 ±0.77	1.16 ±0.79	0.0956
	6 Months	1.27 ±0.70	1.20 ±0.86	0.4547
Nyctalopia	**BV**	1.8 ±1.37	1.516 ±1.061	0.5881
	3 Months	1.5 ±1.16	1.500 ±0.9738	0.5289
	6 Months	1.39 ±1.06	1.419 ±0.9583	0.5077
Hamarlopia	**BV**	1.63 ±1.24	1.23 ±0.61	0.2299
	3 Months	1.4 ±0.93	1.13 ±0.62	0.1537
	6 Months	1.20 ±0.49	1.13 ±0.63	0.4598
Glaring of light	**BV**	2 ±1.41	2.23 ±1.45	0.4441
	3 Months	2.16 ±1.36	2.17 ±1.44	0.9258
	6 Months	1.62 ±1.01	2.16 ±1.42	0.1244
Colored halos	**BV**	1.1 ±0.40	1.06 ±0.35	0.7416
	3 Months	1.16 ±0.37	1.10 ±0.48	0.4890
	6 Months	1.10 ±0.30	1.10 ±0.48	>0.999
Visualization of Non-existing things	**BV**	1 ±0	1 ±0	>0.999
	3 Months	1 ±0	1 ±0.26	>0.999
	6 Months	1.03 ±0.18	1 ±0.27	>0.999

14.4Safety Assessment:

14.4.1 Assessment of Adverse event and Serious Adverse Event:

In both Isotine Group and Control group, 3 AEs were reported. The AEs reported were Right Upper Lid Stye, Excessive Tearing, Cough, Chikungunya, Constipation, Irritation in Eyes.Out of the 3 AEs in the Isotine Group, 2 were unrelated to the study drugs whereas 1 were probably related to the study drug. The details are presented in table 9.

Table 9: Assessment of adverse event

Group	Total AE	Unrelated	Unlikely	Possible	Probable	Definite
Isotine Group	03	02	0	0	01	0
Control Group	03	03	0	0	0	0

Two subjects reported of SAE in the study in Isotine group. The SAE reported was Carcinom a Tongue (Tongue Cancer) and Chikungunya for which subject required hospitalization. The SAE was not related to the study drug or procedure. Also 2 subjects reported to have SAE in the control group. The SAE reported were Laser Cataract Surgery and Facture for which subject required hospitalization.

14.4.2 Assessment of effect of study drug on Vitals:

All the vitals i.e. pulse, respiratory rate, systolic and diastolic BP and temperature were within normal limits before and after the treatment in both the groups. When compared between the groups, no statistically significant difference was observed. The details are presented in table 10.

Table 10: Effect of study drug on Vitals

		Isotine Group		Control Group		P- Value between groups
		n	Mean ±SD	n	Mean ±SD	
Pulse	BV	29	77 ±7.42	31	75 ±6.94	0.2854
	3 Months	28	77.29 ±6.44	28	76.89 ±5.99	0.8141
	6 Months	28	75.96 ±5.52	29	76.10 ±4.39	0.5608
RR	BV	29	16.86 ±2.23	31	16.84 ±1.93	0.8696
	3 Months	28	17.21 ±2.37	28	16.96 ±1.87	0.7497
	6 Months	28	16.68 ±1.94	29	16.55 ±2.02	0.9904
Temp	BV	30	97.78 ±0.37	31	97.86 ±0.41	0.2251
	3 Months	28	98 ±0.30	27	97.98 ±0.24	0.6871
	6 Months	28	98.08 ±0.22	29	98.06 ±0.24	0.8092
Sys BP	BV	30	124.3 ±10.28	31	124.3 ±13.27	0.7595

	3 Months	29	122.1 ±10.25	28	122.4 ±12.52	0.5962
	6 Months	28	121.1 ±11.48	29	123.6 ±10.52	0.2766
Dia BP	BV	30	81.47 ±7.50	31	78.84 ±8.92	0.2365
	3 Months	29	79.59 ±8.0	28	78 ±7.13	0.6868
	6 Months	28	78.57 ±8.50	29	79.31 ±7.13	0.9389

14.4.3 Assessment of comparative change in global assessment for overall change by the investigator and the subject

14.4.4 The table below (Table no 11) shows the overall change on CGI scale as per the investigator and as per the subject. A total of 9 subjects (30%) showed improvement while 19 subjects (63.33%) did not show any change as per the investigator in Isotine group. 1 subject each showed minimal and much worsening in Isotine group. As per the subjects assessment, 18 subjects (60%) did not show any change while 10 subjects (33.33%) showed minimal to much improvement in Isotine group. 2 subjects showed minimal worsening.

In the control group both the investigator as well as subject reportde of no change in 26 subjects (83.87%) while 1 subject showed improvement. 2 subjects (6.45%) in control group showed minimal worsening while 1 subject each showed much and very much worsening.

Table 11: Assessment of overall change on CGI scale

	Isotine Group (N=30)		**Control Group (N=29)**	
	Investigator	Subject	Investigator	Subject
0 = Not assessed	0 (00.00%)	0 (00.00%)	0 (00.00%)	0 (00.00%)
1 = Very much improved	0 (20.00%)	0 (23.33%)	0 (00.00%)	0 (00.00%)
2 = Much improved	6 (20%)	7 (23.33%)	0 (00.00%)	0 (06.90%)
3 = Minimally improved	3 (10.00%)	3 (10%)	1 (3.22%)	1 (3.22%)
4 = No change	19 (63.33%)	18 (60.00%)	26 (83.87%)	26 (83.87%)
5 = Minimally worse	1 (3.33%)	2 (6.66%)	2 (6.45%)	2 (6.45%)
6 = Much worse	1 (3.33%)	0 (00.00%)	1 (3.22%)	1 (3.22%)
7= Very much worse	0 (00.00%)	0 (00.00%)	1 (3.22%)	1 (3.22%)
Total	30 (100%)	30 (100%)	31 (100%)	31 (100%)

14.4.5 Global assessment of overall Safety (Tolerability):

In Isotine group, as per investigators assessment, 28 (93.33%) subjects reported Excellent Overall safety, 2 (06.67%) subject was reported Good Overall safety, whereas per subject's assessment, 28 (93.33%) subjects reported Excellent Overall safety, 2 (06.67%) subject was reported Good Overall safety. The details are presented in table 12.

Table12: Assessment of overall Safety:

Isotine Group	By Investigator	By Subject
1 = Excellent Overall safety	28 (93.33%)	28 (93.33%)
2 = Good Overall safety	2 (06.67%)	2 (06.67%)
3 = Fair Overall safety	0 (00.00%)	0 (00.00%)
4 = Poor Overall safety	0 (00.00%)	0 (00.00%)
Total	30 (100%)	30 (100%)

15. CONCLUSION:

The present study concludes that regular use of Isotine eye drops in a dose of 2 drops twice daily for a period of 6 months helps in the management of cataract. Opthalmic assessment by Slit lamp examination and direct and indirect opthalmoscopic assessment showed improvement in the grade of cataract with the use of Isotine drops as compared to conventional management. Also the number of subjects showing improvement in their condition of cataract was found to be significantly higher with the use of Isotine Eye drops. Visual acuity was also found to be improved with the use of Isotine Eye drops. Isotine eye drops was found to be safe on regular long term use without producing any adverse effects.

Further studies with larger sample size with the use of advanced testing methods for cataract assessment are required to validate the results of the study.

17. REFERENCES:

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18. ANNEXURES:

1. Subject details
2. Randomization List
3. Adverse event record
4. Statistical output