

INTERIM REPORT OF IPLEX USAGE FOR TEN ALS PATIENTS:

The original terms established for those patients admitted into the Trial for Experimental Usage of Iplex (Mecasermin Rinfabate, rhIGF-1/rhIGFBP-3) required an evaluation to be prepared and submitted at the end of the first year of usage. This interim report has been prepared for the following reasons:

1. Because the average life span of an ALS patient is between 2 to 4 years post diagnosis, the ALS patient population has been persistent in their inquiries about the status of IPLEX, whether it is feasible or even advisable to be used.
2. The anxiety and stress level of the ALS patient population is extremely high, leading to an even greater worsening of symptoms. Providing information sooner rather than later appears to be the more humanitarian and compassionate approach to take.
3. Patients currently taking Iplex have asked that an evaluation be done sooner rather than later. Those few admitted into this clinical trial feel an obligation to the rest of the ALS community to be as forthcoming with information as is possible.

Therefore, the following interim report of results is being provided.

Results:

During the 30-week period of Iplex usage that comprised the first half (26 week study period and follow-up four-week confirmation period) of the one year authorized investigational new drug trial, there was a remarkable parity between the apparent responsiveness of the individual patients compared to the aggregated group of patients at large. Symptoms monitored for their absence, presence, or their degree of severity included the following: Hyperreflexia; Tongue Movement; Swallow; Hand Strength; Shoulder Strength; Fatigue; Clonus; Nausea; Atrophy; Breathing; Lability; Lower Arm Strength; Fasciculations; Dizziness; Cramps/Pain; Weakness; Balance; Speech; Upper Arm Strength; Tremor/Palsy; Rigidity; Libido. In the consolidated 30 week period, individual symptoms showed a maximum decline of 9% (Balance) followed by 6% (Tremor/Palsy). The maximum improvement of an individual symptom was 39% (Fasciculations) followed by 28% (Fatigue). The critical function (Swallowing) improved by 25% and Breathing improved by 1%. Compared to the normal relentless worsening in virtually all symptoms over any continuous 30-week period of time, the use of Iplex appears to have stabilized, if not improved, the condition of its users. Those using Iplex demonstrated an average improvement of symptoms of 9.3% (all symptoms combined) after the 30-week period. There were no adverse events or serious adverse events during the 26-week study period. During the four week confirmation period, two serious adverse events occurred: one death from apparent unrelated to Iplex usage in week 28 and one death from apparent unrelated to Iplex usage in week 30.

The structure of the investigational new drug trial did not allow for the use of a double blind placebo controlled study. Further, the use of an historical control was assumed to be of less veracity than the carefully scrutinized observations of the patients themselves, supported by caregiver observation and the supervising investigator.

Associated issues of limited supply of Iplex by the manufacturer Insmad and extremely high cost associated with the use of Iplex other than when it is provided without charge to the patient as part of this investigational new drug trial remain. Therefore, continuing supply and patient cost continue to be obstacles that must be resolved prior to Iplex becoming a viable resolution for the ALS community. We urge that FDA greater oversight and or other potential manufacturing alternatives be quickly and purposefully explored in order to maximize the benefits of Iplex usage by middle- and late-stage ALS patients.

Mecasermin Rinfabate (IGF-1/IGF-bp3) For Amyotrophic Lateral Sclerosis: Notable stabilization and mild improvement shown by subject determination and investigator confirmation

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Protocol Title and Purpose:

Trial for Experimental Usage of Iplex (Mecasermin Rinfabate, rhIGF-I/rhIGFBP-3)
For Patients with Amyotrophic Lateral Sclerosis (ALS).

The purpose for this protocol was to evaluate the applicability of the drug Iplex for use in patients with this severe form of neurodegenerative disease (ALS) and to document the effects of that drug on this select cohort of patients. The drug has previously been approved for, and widely used in, the treatment of growth deficiencies in children. Iplex (rhIGF-I/rhIGFBP-3) has been approved by the FDA for use in patients with severe primary insulin-like growth factor-I deficiency (IGFD). The usage of this medication for the treatment of ALS has not been previously established or approved.

The Principal Investigator for this study was Michael E. Schafer, M.D., Medical Director of ALS WORLDWIDE, Madison, WI, USA. Dr. Schafer was also responsible for monitoring patients on this study, with assistance from others as necessary, including local medical doctors or other care-givers as were involved with the care of a given patient.

The medical expert for this trial was the same as the PI or sponsor, Michael E. Schafer, M.D. The primary sites for the study were Madison, WI and Chicago, IL. Clinical laboratories were used as needed to assess blood values on a periodic or as-needed basis. No one specific laboratory facility was designated, but rather one or more laboratories located convenient to the patient were used. Laboratory studies were paid for by each patient or that patient's insurance payer.

Background Information:

The investigational product was Iplex (Mecasermin-Rinfabate), rDNA origin, injection. It is a preparation containing human insulin-like growth factor – 1 (rhGF-1) produced by recombinant DNA technology. It has had widespread use in the treatment of children with certain forms of growth disturbances and is well established in that patient population. Please see linked package insert for further details on this drug and usage.

There has been incidental and anecdotal experience with the use of this drug in the treatment of patients with amyotrophic lateral sclerosis (ALS) also known as Lou Gehrig's Disease. However, to date there has been very little published about this application. This study was undertaken to evaluate the benefits, if indeed there are such, to this population of patients for which there is virtually no other known treatment to offer. (Please refer to attached list of references for related data and materials.)

The Practice Parameter of the American Academy of Neurology suggests certain guidelines for evaluating a number of body functions and physiological concerns that are affected in ALS. Historically, a number of treatments have been employed, but these are almost entirely used for the relief of symptoms. There is no known treatment, whether drug or other intervention, which can stop entirely the progression of the disease or that can affect a "cure". With this in mind, the present study was designed to evaluate what is anticipated (based on preliminary experience in limited applications) to be positive effects in the slowing or stabilizing of the progression of the disease.

Known potential benefits (again based on very early clinical experience) includes the following: improvement of speech, ease of breathing, greater facility in swallowing and thus in eating and drinking, better control of head movement, weight gain and improved general sense of well-being. Known potential risks include allergic-type reactions to any of the materials contained in the preparation, uncertain and/or unpredictable effect in the presence of neoplasm, and the one most-commonly reported, hypoglycemia

(low blood sugar). This last item has been noted in as many as 40% of previous study groups, but almost without exception has had mild to moderate adverse effects which respond quickly to appropriate treatment. It was felt that most of this risk can be eliminated or at least significantly reduced by the timely ingestion of food or drink immediately before or after the administration of the drug. Naturally, all patients involved in the study were made aware of these anticipated benefits as well as potential risks or complications.

The package insert for Iplex from pediatric studies states hypoglycemia was reported in 11/36 (31%) patients in the study generally rated as mild and asymptomatic. Four hypoglycemic episodes were characterized as symptomatic including two cases that required acute intervention.

Caregivers monitored any potential injection side effects such as injection site reaction and hypoglycemia (signs and symptoms) as well as course of action to take in response to side effects. Monitoring for hypoglycemia is especially important at study drug initiation and when the dose is increased. Caregivers were instructed to always keep a source of sugar available such as orange juice, candy, milk, or glucose gel.

Research Plan:

This drug Iplex (Mecasermin Rinfabate) has been determined by the manufacturer to be best administered by injection (ONLY) in the subcutaneous tissue of the body, dosage determined based on body weight, and given once daily. The Product Insert for rhIGF-I/rhIGFBP-3 recommends starting rhIGF-I/rhIGFBP-3 at 0.5mg/kg and titrating the dose into the therapeutic range of 1.0 to 2.0 mg/kg/day with a maximum dose of 2.0 mg/kg/day while monitoring symptoms. In the severe primary IGFD clinical study, titration to the therapeutic dose occurred over a week timeframe.

Injections were given before a meal and at approximately the same time every day.

The patient population for this study were adults, all age 18 years or older, who have been diagnosed with amyotrophic lateral sclerosis (ALS), selected based upon the date of March 6, 2009, by which time each individual IND was received by the FDA.

This trial was conducted in full compliance with the protocol and all applicable regulatory requirements.

Objectives of the Study:

To administer the drug Iplex (Mecasermin Rinfabate) to patients with ALS and monitor the positive and negative effects of this drug on a patient population for whom there is no other known treatment. The course of this disease is uniformly fatal. Preliminary early evidence in clinical observation in a limited number of cases has suggested an amelioration of the disease or a slowing of the progression of the disease. It was the express purpose of this study to afford all FDA approved patients with the diagnosis of ALS the use of this medication and to monitor any and all effects of its usage.

Trial Design:

Patients enrolled in this trial were evaluated and documented as to the status of the disease prior to the initial injection according to the SPIND CRF Pre-Treatment Form. Information gathered included present age and date of birth, age at diagnosis, any medications currently taken and for what purpose, general state of health, specifically matters relating to the disease of ALS: muscle tone and function; ease of respiration, ability to eat, speak, ambulate, move limbs; body weight at diagnosis and at the time of the initial injection. All such information was tabulated and entered into the patient's own personal file and into the general study file, all in compliance with the standard assessment forms under preparation at the time of starting this protocol.

Patients were started on the medication according to the dosing noted above in section Research Plan. Drug was provided by manufacturer/distributor at no cost to the patient; the patient was notified of any change to this arrangement.

Patients were re-evaluated at 30-day intervals, with monitoring of the same factors noted above and the Interim Visit assessments listed. Any changes, noted benefits or adverse effects were noted and documented according to the SPIND CRF Interim Treatment Form.

The design of this trial was to note and record the effects of the trial drug on the trial population. Each enrolled patient was given the same drug in appropriate dosage/amounts.

Objective measures were used to judge the effect of the drug, such as weight gain or loss; recording of vital signs, especially pulse and respirations; and various muscle functions. Some subjective bias was unavoidably part of the assessment, such as ease of body functions.

The dosage regimen is outlined above, and will apply for the duration of the trial. Trial period will continue for a minimum of one year, or for as long as patient need exists. The drug arrived as prepared by manufacturer/distributor, in liquid form and properly labeled and was administered by a trained caretaker at home. Package insert was attached for further details and description.

Subcutaneous Injections were given one time daily by a trained caregiver. The caregiver was trained to give subcutaneous injections by the study doctor or staff. Injections were given according to guidelines in the Patient Instructions for Use. Injection sites were rotated (upper arm, upper thigh, stomach, buttocks) and injections were never given into areas where the skin is tender, bruised, red, or hard. Injections were not given in the same place two times in a row. The new injection site was at least 1 inch from old injection sites.

Stopping rules were based on observation of effect of the medication on each patient. Patients were advised especially as to potential risks, complications, or adverse effects. Remedial action was based on the severity of the incident and risk versus benefit ratio. Participation by each patient in this trial was strictly voluntary and could have been terminated at any time by the expressed wish of the patient.

The drug was delivered to the pharmacy near the home of the patient and each patient and/or caretaker was responsible for maintaining and accounting for the drug provided.

The inclusion criterion for this initial time period was limited to those patients whose Emergency Compassionate Care IND forms were reviewed and approved by the FDA. Exclusion criterion was not applicable.

Patient Participation:

Patients were able to withdraw at any time. All information gathered prior to withdrawal was kept as part of the trial study. No carry-over from this study for follow-up treatment is anticipated. No patient withdrew permanently; however one patient did stop for a period of 6 weeks, then resumed.

There were no anticipated limitations on any other medications or treatments, before or during trial, which the patient might have been using. Patient compliance was based largely on observation by the respective caretaker and subsequent reporting to the sponsor/investigator.

Amount of Efficacy:

The ALS revised functional rating scale (ALSFRS-R) was used as the principal guideline for assessing benefit or effect of the drug on each patient. This assessment record complied with standard forms presently being developed for future trials. It is recognized as an important indicator of survival and is most often a component of ALS clinical studies. The overall assessment of this study has much to do with the subjective evaluation and recording of quality of life (QOL) issues. Documentation of these

various parameters was done on a weekly basis, by the caretakers, with a formal assessment by the patient, treating physician and Principal Investigator performed every 30 days.

Safety Issues:

Safety was discussed with each patient and caretaker/guardian at the outset of the trial period, prior to any medication being given, and was reviewed intermittently during study. Principal safety factors have to do with possible side effects of the drug in an individual patient. The most common or likely of the unwanted effects is hypoglycemia. The symptoms of hypoglycemia were described in detail to the patient and caregiver prior to beginning treatment. To avoid its occurrence, patients were instructed always to eat a high sugar snack or meal immediately before or immediately after the administration of medication; furthermore each patient (and/or caretaker) was instructed to always have orange juice or other high-sugar drink available for use should the symptoms of hypoglycemia appear. Review with all patients included the studies requested to be included in the Informed Consent Form, especially those relating to negative effect.

The patient was monitored for symptoms of hypoglycemia including dizziness, headache, tiredness, restlessness, shakiness, irritability, trouble concentrating, sweating, nausea, fast or uneven heart rate, flush skin, and weakness. Patients were also monitored for severe hypoglycemia events including fainting, seizure (convulsions), or death.

The documentation of adverse effects by necessity depended on word of mouth reporting by patient or caretaker. Follow-up was determined on ad hoc basis, depending on the nature of the event. All such reports (A.E.'s) were noted by patient and/or caretaker and immediately reported to study investigator. All such events were recorded in patient's personal file and in general study file. Medical examination was done if indicated by the attending physician, and personal monitoring to ensure cessation of adverse event. When further follow-up was indicated, the attending physician provided it.

Adverse events (AE) and Serious Adverse Events (SAE) were documented and reported to the FDA and IRB in compliance with the Code of Federal Regulations.

A clinical trial adverse event is any untoward medical event associated with the use of a drug or drug delivery system in humans, whether or not it is considered related to the drug or drug delivery system. The patient was followed until the event was resolved or explained.

The patient's pre-existing conditions, including clinically significant signs and symptoms of the disease under treatment in the study were documented. After signing the ICF, any change in pre-existing conditions and the occurrence and nature of any AEs were documented.

Serious adverse event (SAE) is any adverse event that results in one of the following outcomes:

- Death
- Initial or prolonged inpatient hospitalization
- A life-threatening experience (that is, immediate risk of dying)
- Persistent or significant disability/incapacity
- Considered significant by the investigator for any other reason

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug events when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

SAEs occurring after the patient has taken the last dose of study drug was collected for 30 days after the last dose of study drug, regardless of the investigator's opinion of causation. Thereafter, serious adverse events were not required to be reported unless the investigator felt the events were related to the study drug.

Number of Subjects in Study:

Initially seven patients (Emergency IND) were enrolled with the opportunity for an additional 30 other patients if circumstances presented themselves. Three additional patients agreed to provide data for inclusion in the study while maintaining individual IND's. Therefore, a total of 10 patients are included in this study. Termination of the trial shall be based upon mutual agreement by all parties involved. All subjects were included in the final evaluation and analysis, i.e. all were treated subjects and thus fell in that category.

Monitoring of records and data:

The investigator/sponsor agreed to all monitoring and/or audits by regulatory agencies and agreed to make all data available as appropriate. The study is and remains small and will remain under the control of the FDA and the investigator/sponsor that shall be responsible for quality control and quality assurance.

Ethics:

The principal ethical consideration involved in this study was that those individual patients with the diagnosis of ALS whose IND's were approved by the FDA, were to be given the opportunity to receive Iplex, the only medication believed to slow the progress of this disease and improve the symptoms. Every effort was made to be fair and objective in the inclusion of patient subjects and in their treatment throughout the trial period.

Data handling and record-keeping was done by the investigator/sponsor Michael E. Schafer, M.D., with the assistance of Stephen Byer, Barbara Byer and Lorie Walker.

The drug was offered for no charge to the patient by the manufacturer, Insmmed Corporation. Any anticipated change to this agreement will be submitted to all involved parties.

It is anticipated that either during or at the termination of the study the results shall be offered for publication in a peer-reviewed medical/scientific journal.

Additional Documents:

Individual Patient Summary Results

Test Data Summary

Package Insert for IPLEX, including drug use, storage and handling attached.

ALSFRS-R scale