Nova Laboratories Limited

CLINICAL TRIAL PROTOCOL

PRODUCT:	Oral Liquid 13-cis-retinoic acid (13-CRA)
PROTOCOL NUMBER:	INV500
VERSION NUMBER:	Version 5.0
DATE:	08 Dec 2017
TITLE:	**Relative bioavailability and comparative pharmacokinetics of 13-CRA oral liquid and extracted capsule formulations: a randomised, open label, multi-dose, cross-over clinical trial in patients requiring treatment cycles of 13-CRA.**
	My-CRA (SHORT TITLE)
PHASE OF DEVELOPMENT:	Phase II
TRIAL DESIGN:	An open label, randomised, multiple dose, cross-over relative bioavailability and pharmacokinetics trial of oral 13-CRA liquid and extracted capsule formulations administered to patients from 0 months – < 21 years.
TEST PRODUCT:	1. Oral liquid formulation of 13-Cis Retinoic Acid – test product. 2. Isotretinoin capsules (extracted per standard of care)– reference product. The dose administered will be 200mg/m^2/day for both test and reference product. Patients with a body weight of ≤12kg will receive a dose of 160 mg/m^2.
DURATION OF TREATMENT:	Two months.

Sponsor
Nova Laboratories Limited, Martin House, Gloucester Crescent, Wigston, Leicester, LE18 4YL

Additional Grant Funding from:
Department of Health and the Wellcome Trust

ADMINISTRATIVE STRUCTURE

Lead-Applicant on Wellcome Trust Grant Pharmacokinetics Modeller	[redacted]
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Clinical Trial Management and Monitoring	
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Statistics	
Bioanalysis and Pharmacokinetics	
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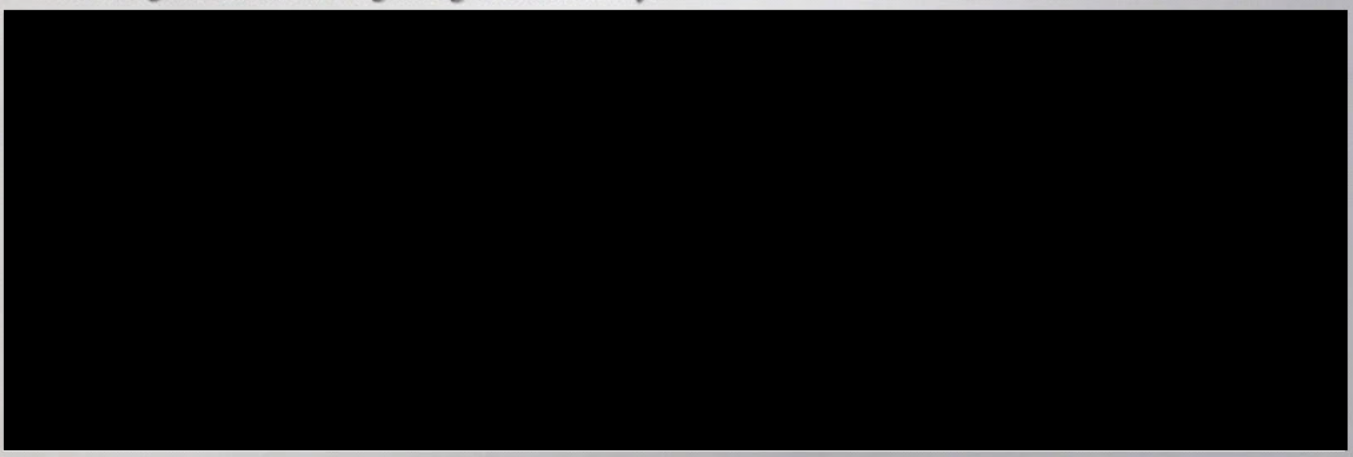
CRO/Pharmacovigilance	

SPONSOR SIGNATURE SHEET

The signature below constitutes approval of this protocol by the signatory and provides the necessary assurances that this survey will be conducted according to all stipulations of the protocol including all statements regarding confidentiality and to local law and regulations.

MEDICAL ADVISOR SIGNATURE SHEET

The signature below constitutes approval of this protocol by the signatory and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol including all statements regarding confidentiality.



STATISTICS SIGNATURE SHEET

The signature below constitutes approval of this protocol by the signatory and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol including all statements regarding confidentiality.

CHIEF INVESTIGATOR SIGNATURE SHEET

The signature below constitutes approval of this protocol by the signatory and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol including all statements regarding confidentiality.

I have read this protocol and agree that it contains all necessary details for carrying out this trial. I will conduct the trial as outlined herein and in accordance with the ethical principles of the Declaration of Helsinki and ICH GCP guidelines. I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this trial. I will discuss the material with them to ensure they are fully informed regarding the drug and the conduct of the trial.
I will only use the informed consent form approved by the sponsor or its representative and will fulfill all responsibilities for submitting pertinent information to the Independent Ethics Committee (IEC) responsible for the trial.

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SYNOPSIS

TITLE	Relative bioavailability and comparative pharmacokinetics of 13-CRA oral liquid and extracted capsule formulations: a randomised, open label, multi-dose, cross-over trial in patients requiring treatment cycles of 13-CRA.
TRIAL NUMBER:	INV500
FINAL PROTOCOL DATE:	Version 5.0 : Dated: 08 December 2017
PHASE:	II
SPONSOR:	Nova Laboratories Limited Martin House, Gloucester Crescent, Wigston, Leicester, LE18 4YL,UK
SENIOR CLINICAL ADVISORS **PRINCIPAL INVESTIGATOR/** **PLANNED TRIAL SITES:** **(Trial sites will be approved for initiation, full site initiation will take place when a suitable patients is identified)**	[redacted]
TEST PRODUCT:	Oral liquid formulation of 13–Cis Retinoic Acid
REFERENCE PRODUCT:	Isotretinoin capsules (extracted per standard of care guidelines)
DOSE:	The dose administered will be 200mg/m^2/day for both test and reference product. Patients with a body weight of ≤12kg will receive a dose of 160 mg/m^2.
OBJECTIVES:	*Primary objective:* To determine the relative bioavailability and pharmacokinetics of 13–CRA administered as oral liquid and extracted capsule formulations. *Secondary objectives:* To determine the safety and tolerability. To assess palatability and acceptability.
TRIAL DESIGN:	An open label, randomised, multiple dose, cross-over relative bioavailability and pharmacokinetics trial of oral 13–CRA liquid and extracted capsule formulations administered to patients from 0 years – < 21 years.
SAMPLE SIZE:	Up to 20 patients, both male and female, aged 0 years to < 21 years of age will be recruited: A minimum of 4 subjects will be enrolled in the 0 to < 2 years age group and 4 subjects in the 2 to < 6 years age group.
INCLUSION CRITERIA:	1. Male or female aged from 0 years to < 21 years of age. 2. Patient with high risk neuroblastoma, or unresectable, unfavourable histology intermediate risk neuroblastoma the latter age ≥ 18 months at diagnosis 3. Patient who is scheduled to receive at least two treatment cycles of 13-CRA. 4. Patient who cannot swallow 13-CRA capsules (i.e. requires extraction of 13-CRA from the capsules). 5. Negative pregnancy test for females of child-bearing potential no

<table>
<tr><td></td><td>more than seven days before initiation of treatment, and sexually active patients and partners agreeing to undertake adequate contraceptive measures (see section 4.5).
6. Provision of a single or double lumen central venous catheter for sampling (i.e. already in place).
7. Parent(s)/legal guardian able and willing to provide written informed consent for the patient to take part in the trial.
8. Where applicable, the patient should assent to undergo blood sampling for pharmacokinetic purposes and to allow physiological measurements to be made.</td></tr>
<tr><td>EXCLUSION CRITERIA:</td><td>1. Any clinically significant medical condition or abnormality, which, in the opinion of the investigator, might compromise the safety of the patient or which might interfere with the trial.
2. Diagnosis of high-risk neuroblastoma (HRNBL) which is currently being treated on the SIOPEN HRNBL trial (patients who have exited this trial will be eligible).
3. Known allergy to 13-CRA or any of the excipients.
4. Inadequate contraception measures in females of childbearing age.
5. Receiving concomitant treatment with tetracyclines.</td></tr>
<tr><td>CRITERIA PRIOR TO STARTING EACH CYCLE OF 13-CIS-RA</td><td>1. Total bilirubin ≤ 1.5 x normal, and (SGPT) ALT ≤ 5 x normal. Veno-occlusive disease if present, should be stable or improving.
2. Skin toxicity no greater than CTCAE Grade 1[10]
3. Serum triglycerides <5.65mmol/L.
4. No haematuria and / or proteinuria on urinalysis.
5. Serum calcium ≥ 2.0mmol/L to ≤ 2.9mmol/L.
6. Serum creatinine based on age / gender as follows:
<table>
<tr><td>Age</td><td colspan="2">Maximum Serum Creatinine µmol/L</td></tr>
<tr><td></td><td>Male</td><td>Female</td></tr>
<tr><td>1 month to < 6 months</td><td>35</td><td>35</td></tr>
<tr><td>6 months to < 1 year</td><td>44</td><td>44</td></tr>
<tr><td>1 to < 2 years</td><td>53</td><td>53</td></tr>
<tr><td>2 to < 6 years</td><td>70</td><td>70</td></tr>
<tr><td>6 to < 10 years</td><td>88</td><td>88</td></tr>
<tr><td>10 to < 13 years</td><td>106</td><td>106</td></tr>
<tr><td>13 to < 16 years</td><td>132</td><td>124</td></tr>
<tr><td>≥ 16 years</td><td>150</td><td>124</td></tr>
</table>
7. Patients with a seizure disorder must be well controlled and taking anticonvulsants. CNS toxicity < grade 2 (CTCAE).</td></tr>
<tr><td>WITHDRAWAL CRITERIA:</td><td>1. Positive pregnancy test - pregnancy testing will be undertaken no more than seven days before treatment commences and routinely no more than seven days before each course of treatment in females of childbearing potential. If a patient is found to be pregnant during the trial, the next course of treatment will not be given until the pregnancy has been discussed with the treating clinician, and the patient will be withdrawn from the trial whether or not treatment is continued.
2. Request of the patient, for any reason.
3. Discretion of the investigator.</td></tr>
<tr><td>TREATMENT STRATEGY:</td><td>All patients requiring at least two cycles of 13–CRA therapy will be eligible for recruitment into the trial.

13–CRA will be prescribed to patients according to local treatment protocols at each clinical site. The dose administered will be 200mg/m^2/day for both test and reference product. Patients with a body weight of ≤12kg will receive a dose of 160 mg/m^2.

The pharmacokinetics of 13–CRA liquid (test product) and extracted capsule (reference product) will be evaluated over two months. Prior</td></tr>
</table>

	to the initiation of 13–CRA treatment as part of the trial, patients will be randomised to receive either liquid or capsule formulation in "My-CRA month 1". The patients will then cross-over to the alternative formulation in "My-CRA month 2". The patients on the trial who require further treatment will revert to standard therapy i.e. extracted capsules according to local practice.
ENDPOINTS:	*Primary Endpoints:* Pharmacokinetic parameters (13-CRA) Primary parameters: • Relative bioavailability • Clearance (CL/F), • Volume of distribution (V/F) Secondary parameters: • Time to maximum concentration (T_{max}), • Maximum plasma concentration (C_{max}), • Area under plasma concentration time curve (AUC), • Half-life ($t_{1/2}$) • Levels of the metabolite 4-oxo-13-cis-RA. *Secondary Endpoints:* Safety parameters • Evaluate the local (oro–pharyngeal) tolerability • Skin toxicity • Hypercalcaemia • Hepatotoxicity • Triglycerides Oro-pharyngeal adverse event data will be listed as adverse events and separately summarised. *Palatability and Acceptability:* Evaluate the taste acceptability of the new oral liquid formulation of 13-CRA.
ADVERSE EVENTS	All adverse events that occur during the duration of therapy will be recorded and reports per regulatory health authority requirements. All serious adverse events (SAEs) will be followed until resolution or stabilisation.
PROCEDURE	It is anticipated that all patients recruited into the trial will have a central line in situ. Patients will attend the site clinic on Pharmacokinetic Trial Days: Month 1: Day 1 and Day 14 Month 2: Day 1 and Day 14 On the day of sampling, 13-CRA (reference or test) will be administered in the clinic by a research nurse. Blood (2 ml) will be sampled post-dose at time points selected as follows:

Time point (h)
0.5 (Day 1 and Day 14)
1
1.5
*2
3
4
5
*6
**24-48 (Day 15 or 16)

	*The 2 hour and 6 hour samples are mandatory, with at least three further samples (where possible) selected over 0.5 to 5 hours. **Sample at 24-48 hours applies only to the final dose administered on Day 14 to allow the elimination phase of 13-CRA to be calculated. For individual patients sampling times should remain the same across each of the four PK days, where possible.
PATIENTS DURATION:	Patients will be administered twice daily doses of 13-CRA for the duration of the trial. Evaluation of the test and reference product will occur over two months of therapy. Individual patient's participation will therefore be for 2 months. The whole trial recruitment period is estimated to be approximately 12 to 18 months from initiation.
STATISTICAL METHODS	The data from all patients taking part in the trial will be pooled and analysed simultaneously to avoid excessive blood sampling. Population pharmacokinetic parameters will be estimated by using a non-linear, mixed effects modelling approach. In the population approach all data from different individuals are fitted simultaneously using a non-linear, mixed effects modelling approach and post hoc individual kinetic parameters can be calculated with as few samples as one per individual. An appropriate software package such as NONMEM will be used to conduct the analysis. Preliminary analyses will focus on the structural and variance models. One and two compartment models with first and zero order inputs will be implemented. Between patient variability will be assumed to be log-normally distributed, and residual error will be modelled using additive, proportional and combined error structures. Adverse events will be coded according to the current version of MedDRA. Reporting of the safety data will be of a descriptive nature and presented using summary statistics. Analysis will be planned and documented in the Statistical Analysis Plan.
Data Safety Monitoring Committee (DSMC)	An independent Data Safety Monitoring Committee will be formed to alert and/or make recommendations to The Sponsor about any existing or potential safety issues.

ABBREVIATIONS

13-CRA	13-Cis Retinoic Acid
AE	Adverse event
AUC	Area under the plasma drug concentration-time curve extrapolated to infinity
AUC_{0-24}	Area under the plasma drug concentration-time curve from zero to 24 hours
C_{max}	Maximum observed plasma concentration
CL/F	Apparent plasma clearance following intranasal administration
CRF	Case report form
CQC	Care Quality Commission
%CV	Coefficient of Variation calculated using $100 \times \sqrt{e^{s^2} - 1}$, where s^2 is the variance of the log transformed data
FBC	Full blood count
GCP	Good clinical practice
GLP	Good laboratory practice
HRNBL	High Risk Neuroblastoma
HR-NBL-1.7/SIOPEN	current treatment trial for HRNBL
IEC	Independent ethics committee
IM	Intramuscular
IMP	Investigational medicinal product
IV	Intravenous
kg	kilogram
LFT's	Liver function tests
MHRA	Medicines & Healthcare products Regulatory Agency
ml	millilitre
NHS	National Health Service
NPSA	National Patient Safety Agency
PD	Pharmacodynamics
PK	Pharmacokinetics
SAE	Serious adverse event
SIOPEN	International Society of Paediatric Oncology Europe Neuroblastoma
Sponsor	Nova Laboratories Limited
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment emergent adverse event
$t_{½}$	The terminal half-life of the drug in plasma
VAS	Visual Analogue Scale
V / F	Apparent central compartment volume of distribution
WHO	World Health Organisation

1. INTRODUCTION

The need for a liquid formulation

Neuroblastoma (NBL) is an aggressive cancer that predominantly affects children aged 5 years or less. It is an orphan disease (incidence ~ 10 cases per million children; 1 case per 500,000 general population) that still has poor outcomes.

Children who present with metastatic NBL (approximately 50% of cases) are most commonly treated with myelo-ablative chemotherapy followed by stem-cell rescue and, to eradicate 'minimal residual disease' post rescue, 13-cis-retinoic acid (13-CRA, isotretinoin) usually alongside immunotherapy. Given by the enteral route, at a dose of 80 mg/m^2 twice daily, in 2-week cycles for 6 months 13-CRA has been shown in clinical trials to improve event-free survival. Thus, most clinicians accept 13-CRA as frontline therapy for patients with NBL in remission.

However, 13-CRA is not licensed for NBL in any region or country in the world and is currently available only as a gelatin capsule that children are often unwilling and / or unable to swallow. Presently, carers have to 'open' capsules of 13-CRA, and squeeze the contents into foods. As few young children will take capsules, carers often have to administer 13-CRA by first extracting liquid out of the capsule. Studies show that the current method of administration results in marked variability in drug exposure between patients and significantly lower plasma concentrations in patients receiving the extracted drug as compared to those able to swallow the capsules whole (1). Furthermore, since 13-CRA can cause birth defects, pregnant women (e.g. parent of a child with NBL) risk accidently exposing their unborn babies when extracting 13-CRA from capsules.

No manufacturer has yet developed a child-friendly preparation of 13-CRA. Nova Laboratories Limited is developing a new oral liquid dosage form of 13-CRA, which will facilitate more consistent and accurate dosing and improve palatability for children.

This trial aims to investigate the relative bioavailability and comparative pharmacokinetics of the new oral liquid and existing capsule formulations of 13-CRA in patients. Any patient requiring at least two treatment cycles with 13-CRA will be eligible for the trial. The local oropharyngeal tolerability, the palatability and acceptability of the formulation will also be assessed.

The trial will be conducted in compliance with the protocol, ICH GCP and the applicable regulatory requirement(s).

Liquid formulation of 13-cis-retinoic acid

13-CRA is a derivative of vitamin A. It induces differentiation and growth arrest of malignant NBL cells *in vitro* through binding to retinoid acid receptors and altered gene transcription (2). Currently, the only licensed formulation of 13-CRA is a gelatin capsule with an indication for severe acne.

In patients with NBL the optimal therapeutic blood level for 13-CRA is thought to lie between 2-10 μM (3,4,5). At blood concentrations above 10μM, there is an increased frequency of toxicity reactions (6). Studies indicate that children able to chew and / or swallow 13-CRA capsules are significantly more likely to achieve target concentrations than those who have the drug extracted from capsules prior to administration. Hence, 'method of administration' is a key factor in achieving adequate blood levels of 13-CRA. Since dosing with 13-CRA is not adjusted according to blood levels, inherent variability in dose delivery associated with extracting drug from capsule runs the risk of under- and over- dosing of drug (1). A child appropriate oral liquid formulation of 13-CRA should reduce inter- and intra- patient variability in blood 13-CRA levels

currently seen in patients dosed using the "drug extraction method". Since 13-CRA is a known teratogen, women of childbearing age are required to have a negative no more than seven days test prior to starting 13-CRA and use of effective contraception during therapy and for 3 months after cessation of treatment. The oral liquid product will also not pose the same level of teratogenic risk for mothers who currently have to extract drug from capsules. Hence, an oral liquid 13-CRA formulation for enteral use would be flexible and child- and carer- friendly. It would also allow for dosing by oral and naso-gastric routes.

Benefits and Risks

The importance and potential benefits of this work to parents, carers and healthcare professionals is clear. The burden of accurately dosing and administering 13-CRA extracted from capsules can only really be described by those intimately involved in this practice. Many healthcare professionals would struggle to perform this task even under ideal conditions.

Any risks associated with taking blood samples from the central line for pharmacokinetic analysis are minimised by following the established aseptic guidelines practiced by the paediatric oncology unit. The number of pharmacokinetic blood samples have been minimised by utilising a sparse sampling population pharmacokinetic modelling approach. However, if the number of samples does cause disruption or irritation to the patient, the patient may be withdrawn from the trial.

Justification for the route of administration, dosage and treatment period

1.1.1. Route

13-CRA is administered during the remission phase in the treatment of HRNBL between cycles of immunotherapy and also in patients with unresectable, intermediate risk neuroblastoma with unfavourable INPC histology and in patients with relapsed and refractory disease who have not already received 13-CRA. It is administered orally, currently using the capsule form licensed for severe acne.

It is clear that many young children will not take solid medicines (tablets, capsules). Potential solutions to this issue include developing a liquid for parenteral use, a medicine to be administered by the rectal route and a transdermal drug. While there are other potential solutions, the oral liquid preparation meets important criteria for this medicine including flexible dosing, ease of use, minimal additional risk to patient and carer and patient comfort.

1.1.2. Dosage

The dose administered is in accordance with approved practice for 13-CRA extracted capsules. This is based on previous studies have shown that the dose obtained from extracted capsules needs to be adjusted to 200mg/m^2/day in order to achieve the same blood level as that seen for capsules that have been swallowed whole (1). Therefore the dose used in this trial will be 200mg/m^2/day for both test and reference product. Patients with a body weight of ≤12kg will receive a dose of 160 mg/m^2.

Patients with HRNBL may be included in the European SIOPEN HRNBL trial (7), which includes treatment with 13-CRA during the maintenance phase. These patients will be excluded from the **My-CRA** trial in order to ensure that the trial endpoints for the SIOPEN clinical trial are not compromised. Patients who are ineligible for the SIOPEN high risk trial, have exited the SIOPEN trial, or patients ≥ 18 months with unresectable, intermediate risk neuroblastoma with unfavourable INPC histology who may benefit from at least two cycles of 13-CRA will be dosed according to the currently approved local guidelines.

1.1.3. Treatment period

All patients requiring 13-CRA therapy, who are unable to swallow 13-CRA capsules, will be eligible for recruitment into the trial.

The pharmacokinetics of 13-CRA liquid (test product) and extracted capsule (reference product) will be evaluated in over a two month period to allow for two cycles of treatment in a cross over design (one test treatment period and one reference treatment period). The 14-day treatment period and two week break between treatment cycles is based upon previous studies (7) and is the standard treatment period for cycles of 13-CRA. If patients require a longer period of time between treatments then this will be acceptable within the visit windows (i.e. treatment period 2 will be within 14 +up to 7 days of completion of treatment period 1).

Prior to the initiation of the trial 13-CRA, patients will be randomised to receive either liquid or extracted capsule formulation in "My –CRA month 1". The patients will then cross-over to the alternative formulation in "My-CRA month 2". After the trial if a patient requires additional cycles of 13-CRA, the patient will revert to standard 13-CRA therapy i.e. extracted capsules according to local practice.

2. AIM AND OBJECTIVES

The aim of this trial is to investigate the pharmacokinetics, safety, tolerability and palatability of oral liquid 13-CRA in patients aged from 0 months – < 21 years.

2.1 Primary objective

- To determine the relative bioavailability and pharmacokinetics of 13-CRA administered as oral liquid and extracted capsule formulations.

2.2 Secondary objectives

- To determine the safety and tolerability.
- To assess palatability and acceptability.

3. TRIAL DESIGN

3.1 Exit points

The normal exit point from this trial will be when the patient completes the follow up of the second treatment period, i.e. when the patient returns to clinic for their next treatment course or for their next clinic review (it is anticipated that this will be approximately two to three weeks following 13-CRA treatment), all adverse events will be followed up to conclusion.

All patients who have at least one blood sample taken for the pharmacokinetic trial will be included in the population pharmacokinetic analysis. If the parent(s)/legal guardian or patient refuses further blood sampling the patient will be withdrawn from the trial.

3.2 Type of trial

This is an open label, randomised, multiple dose, cross-over relative bioavailability and pharmacokinetics trial of oral 13–CRA liquid administered to patients aged from 0-< 21 years. The decision to initiate 13-CRA therapy will be taken independently of this trial protocol. The trial will be conducted in patients who are attending the hospital for treatment for neuroblastoma requiring at least two cycles of 13-CRA. 13–CRA will be prescribed to patients according to the locally approved treatment protocols at a dose of 200mg/m^2/day for both test and reference product. Oral 13–CRA is administered for NBL (this is usually at a dose of 160mg/m^2) for 14 days, every 4 weeks, for 6 months, however where the dose is extracted from capsules this dose

is increased to 200mg/m^2. In this trial the dose of 13-CRA will be 200mg/m^2 as patients able to swallow the capsules will not be recruited to the trial. Patients with a body weight of ≤12kg will receive a dose of 160 mg/m^2. Patients who require their dose through a nasogastric tube or gastromy will be included in the trial, this will be recorded in the case record form.

When an appointment is made for the patient to attend the hospital clinic for initiation of 13-CRA treatment the parent(s)/legal guardian of the patient will be approached to discuss the pharmacokinetic trial and the possibility of the patient's entry into the trial; information regarding the trial may be sent to parents and patients prior to them attending. The parent(s)/legal guardian's consent to take these additional blood samples and record physiological information (local [oro-pharyngeal] tolerability, skin toxicity, adverse events) will be sought. Following parental consent, the patient will be approached and the trial procedures explained to them in order to receive their verbal and/or written assent to participate in the trial, if applicable (usually where the patient is over 7 years of age). Parents and patients may still refuse to participate in the trial at any stage prior to or during their treatment with 13-CRA. Parents and patients will be given as much time as they need to consider participation in the trial. Patients and parents may choose to share information about the research with their family or GP before they decide if they would like to take part in the trial. Investigators will ensure that families have at least 24 hours to consider involvement in the trial. In practice this is likely to be longer as parents and patients are most likely to be approached well in advance of their 13-CRA treatment period. If the parent(s)/legal guardian decide that they would not like their patient to participate in the trial then this will in no way affect the onward care of the patient.

When the patient attends hospital for initiation of 13-CRA treatment, it is anticipated that they will have a central line *in situ*. Patients will attend the clinic on Pharmacokinetic days; these will be Day 1 and Day 14 for each of the trial treatment periods. Blood samples for pharmacokinetic analysis will be taken over the course of six hours after which the patients will leave the clinic. Parents and patients will be asked if they are willing to return for an additional sample at 24-48 hours following their final dose on Day 14 of treatment.

Additional assessments will be made according to the trial procedures (section 4).

A trial schedule is presented in Appendix I.

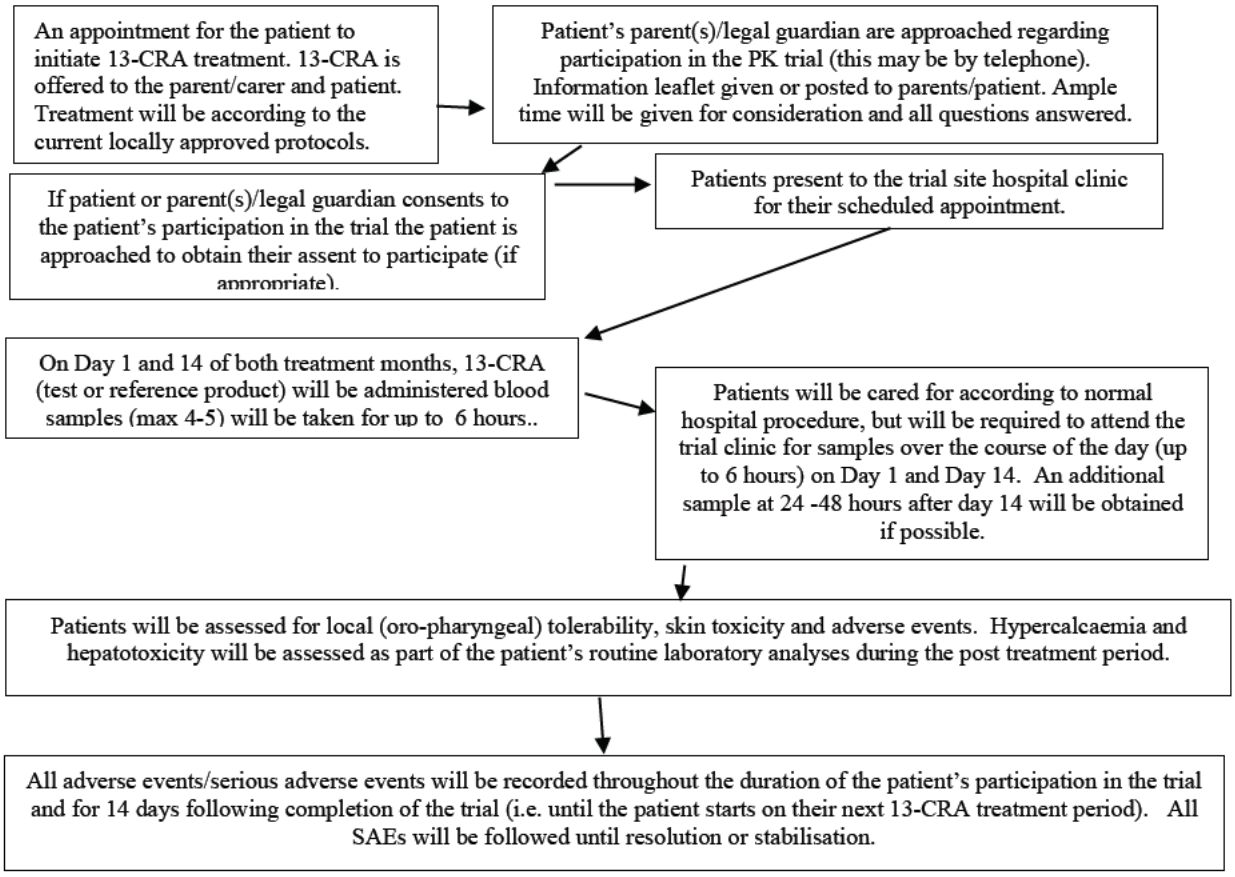
3.3 Expected duration of patient participation

Patients will be administered twice-daily doses of 13-CRA for the duration of the trial. Evaluation of the test and reference product will occur over two months of therapy. Individual patient's participation will therefore be 2 months, including a two-week follow-up.

3.4 Trial schematic and schedule

A trial schematic for individual patients is presented in Figure 3.4 and a full schedule is presented in Appendix I.

Figure 3.2 Trial Schematic for an individual



3.5 Data to be recorded on the case report form

The following data will be recorded on the patient's case report form:

- Unique patient identifier- to identify site and patient number in trial.
- Date of informed consent (and receipt of assent if applicable).
- Demographic data: age, gender, race.
- Weight and height.
- Vital signs: blood pressure, temperature, heart rate (supine pulse rate) and respiratory rate.
- Physical examination.
- Safety laboratory results (taken as part of routine standard care of the patient, relevant results will be recorded in the CRF)
- Relevant non-oncology medical history: relevant past medical history in the four weeks prior to the trial, known allergies and relevant longstanding conditions that are on-going.
- Oncology history (diagnosis) and treatment (over the last month) to include concomitant medication for their indication (i.e. confirmation of eligibility for 13-CRA treatment and current treatment).
- Concurrent medication: any non-oncology medication taken in the month prior to trial.
- Inclusion/exclusion criteria.
- Concomitant medications taken during participation in the trial.
- Dose of 13-CRA (equally divided doses, and daily timing of doses on the trial diary card) – including calculation of body surface area and daily dose required.
- Confirmation of randomisation number, test/or reference treatment and batch numbers.
- Time of treatment.

- Precise time of blood sampling.
- Details of any local oro-pharyngeal tolerability (recorded as adverse events if appropriate). Oro-pharyngeal tolerability will be assessed before and after dosing. Any oro-pharyngeal adverse events will be recorded on the trial diary card.
- Palatability. This will be assessed at Day 14 in the clinic using a palatability questionnaire that will be completed by the patient/patient's parents (depending on the age of the patient).
- Adverse events – all events occurring during the timeframe of the trial and for a period of 14 days afterwards (on the trial diary card).
- Serious adverse events – all events regarded as serious during course of trial and until resolution.
- Trial withdrawal information, if applicable.
- Date and time of trial discharge (i.e. when the patient completes the period of follow up).

4. TRIAL PROCEDURES

4.1 Demography

The following demographic characteristics will be recorded at the visit: age, sex, race, height, weight.

4.2 Medical History

Oncology history and treatment will be recorded to confirm eligibility. Additional relevant medical history during the four weeks prior to the trial will be recorded. This will include all current conditions by diagnosis (where possible) and any concomitant medication.

4.3 Physical Examination

A qualified medical practitioner will carry out a general physical examination. This will involve an external examination of the cardiovascular, respiratory and gastro-intestinal systems. This will be performed at baseline prior to treatment to ensure no concurrent conditions exist that may exclude the patient from the trial.

4.4 Safety Laboratory Assessments

Measurement of the haematological and biochemical parameters will be carried out prior to each course of 13-CRA treatment in line with standard of care. Additional and/or more frequent clinical assessments and laboratory tests may be carried out at the discretion of the investigator in line with standard of care. Safety laboratory tests will not be undertaken as part of the trial protocol, however results of routine laboratory tests may be collected as part of the safety assessment of the two treatment periods. Any findings that the investigator considers to be an adverse event* will be recorded on the case record form (specifically for the following parameters):

- Full blood count including haemoglobin, white blood cell, neutrophil, lymphocyte and platelet counts.
- Renal and liver function (Na, K, Ca, Mg, PO4, urea, creatinine, glucose, total protein, bilirubin, transaminases)
- Serum lactate dehydrogenase (LDH)

* Abnormal laboratory values or test results will generally constitute adverse events only if they induce clinical signs or symptoms or require therapy, although investigators may report any laboratory finding or test result that they consider to be clinically relevant.

4.5 Pregnancy Prevention

For women of childbearing potential all conditions of the Pregnancy Prevention Programme should be met (8). Patients of childbearing potential, their partners and parents must understand and accept the need for effective contraception, be informed and understand the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy. Female patients of childbearing age must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if appropriate. As part of the standard clinical care, female patients of childbearing potential will undergo a pregnancy test no more than seven days prior to the start of treatment and routinely no more than seven days before each course of treatment. Although the likelihood of pregnancy in patients receiving 13-CRA is extremely low, if a positive pregnancy test does result during the trial, the next course of treatment will not be given until the pregnancy has been discussed with the treating clinician, and the patient will be withdrawn from the trial whether or not treatment is continued.

4.6 13-CRA Dosing and Blood sampling for Pharmacokinetic analyses

All patients recruited into the trial will already have a central line *in situ*.

Patients will receive their first morning dose of 13-CRA according to standard practice (for capsules by extracting the medicine from the capsule), or according to liquid dosing instructions, and will include a drink of water (volume to be included in dosing instructions) after dosing. Dosing instructions (including which foods such as yogurt or ice cream can be given with the medicine) for both medicine extracted from capsules and liquid will be provided to the site in a separate dosing manual, this document will be version controlled and retained in the trial files at site.

The pharmacokinetic profile of 13-CRA post dosing will be evaluated.

At least five blood samples (2ml) will be (where possible) taken post-dose at the time-points specified in Table 4.6 below. In patients under two years of age, up to three samples at appropriate sampling times will be taken. Sampling times in the patients under 2 years of age will be discussed with the Sponsor prior to the trial PK sampling days in order to ensure an even spread of sampling times in this younger population of patients. Arrangements will be discussed and agreed in writing (or by email) on an individual basis for this group.

Table 4.6 Blood Sampling Schedule

	Time point (h)	Requirements
	0.5 (Day 1 and Day 14)	*Two and six hour samples are mandatory. At least three further samples will be selected over 0.5 to 5 hours (where possible). **Sample at 24-48 hours applies only to the final dose administered on Day 14 to allow the elimination phase of parent and metabolite(s) to be calculated. For individual patients sampling times should remain the same across each of the four PK days, where possible.
	1	
	1.5	
	2	
	3	
	4	
	5	
	6	
	24-48 (Day 15 or 16)	

Flushing of the central line with normal saline and allowance for dead space will be performed according to local practice.

2.0 ml blood samples will be taken and processed immediately according to the technical manual and laboratory kit provided to the trial staff. This technical manual will be version controlled and retained in the trial files at site

4.7 Vital Signs

At baseline an assessment of vital signs will be made: Systolic and diastolic blood pressure, pulse and body temperature at baseline (in older patients this will be following 5 mins rest in supine position). Following dosing vital signs will be monitored according to routine standard of care, any unexpected measurements will be recorded as adverse events and reported in the normal way.

4.8 Palatability assessments

At the end of each of the two treatment cycles patients (together with their parents) will be surveyed using a standard questionnaire for their views of the palatability and acceptability of the 13-CRA. In the case of patients <6 years of age, the researcher will survey the view of one or both parents. For patients from 6 years of age, the researcher will seek the views of one or both parents and the patient.

The questionnaire will probe the taste and general acceptability (willingness to continue with treatment, ease of dose administration etc.). After five patients have completed the survey the use of the questionnaire will be reviewed, by both the investigator and Nova, to ensure that it is working satisfactorily. If the questionnaire needs to be adjusted (in terms of its administration or the ability/age groups of the patients), then this will be done. Minor amendments only will be made. All minor edits will be documented and a copy of the amended questionnaire will be provided to the Ethics Committee. If significant adjustment is required Ethical Committee Approval will be sought before administering the amended questionnaire.

Data on the following will be collected using a visual (hedonic) analogue scale and verbal responses.

- Taste on first administration
- Residual after taste
- Smell
- Any incidences of spitting medicine out or vomiting
- Willingness to take 13-CRA on a daily basis
- Ease of dose administration using the bottle and oral syringe
- Preference between extracted capsule and liquid medicines

The survey will be conducted by a trained research nurse. The survey will be face to face with patient and/or parent and will be conducted on Day 14 of each treatment cycle and take no longer than 5 minutes. In addition aspects of palatability may be included in the patient diary card if appropriate. Diary cards will be provided to the Ethics Committee for approval prior to use.

4.9 Tolerability assessments

All adverse events will be collected and recorded during the trial and for the 14 day follow up period. Patients and parents will be provided with a trial diary card and will be asked to record adverse events.

Common adverse events associated with 13-CRA include dry or peeling skin, cracked lips and dry eyes, skin may also become more sensitive to sunlight. Therefore these adverse events collected during the trial will be separately listed.

13-CRA can cause some mild changes in liver function and hypercalcemia, therefore standard of care laboratory assessments will be made to monitor liver function and serum calcium levels.

4.10 Oropharyngeal Tolerability

Oro-pharyngeal tolerability and symptoms will be separately assessed. Dry skin, peeling skin, cracked lips and dry eyes will be assessed by the investigator on a four point scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe).

Oro-pharyngeal symptoms will be assessed at baseline and following administration of 13-CRA during the Pharmacokinetic Day 14. Patients and parents will be provided with a diary to record any oro-pharyngeal events during the two weeks treatment. This diary card will be reviewed and discussed with the parents (and patient if appropriate) on Day 14 for each of the treatment cycles. Any local clinically relevant changes will be recorded as adverse events, classified by type of event (e.g. lesion, and/or other) and severity.

5. SELECTION OF PATIENTS

Up to 20 patients will be enrolled into the trial depending on the number of pharmacokinetic blood samples that are obtained from each patient. A minimum of 150 pharmacokinetic blood samples are required for adequate analysis of the patient population.

To ensure each age cohort is appropriately represented by age the trial will aim to include a minimum number of patients to the following age groups:

Age 1 - <2 years: 4 patients
Age 2 - < 6 years: 4 patients

5.1 Inclusion criteria

To be eligible for inclusion into this trial the patients must fulfil all of the following criteria:

1. Male or female aged from 0 years to < 21 years of age.
2. Patient with high risk neuroblastoma, or unresectable, unfavourable histology intermediate risk neuroblastoma the latter age ≥ 18 months at diagnosis
3. Patient who is scheduled to receive at least two treatment cycles of 13-CRA.
4. Patient who cannot swallow 13-CRA capsules (i.e. requires extraction of 13-CRA from the capsules).
5. Negative pregnancy test for females of childbearing potential no more than seven days before initiation of treatment, and sexually active patients and partners agreeing to undertake adequate contraceptive measures (see section 4.5).
6. Provision of a single or double lumen central venous catheter for sampling (i.e. already in place).
7. Parent(s)/legal guardian able and willing to provide written informed consent for the patient to take part in the trial.
8. Where applicable, the patient should assent to undergo blood sampling for pharmacokinetic purposes and to allow physiological measurements to be made.

5.2 Exclusion criteria

To be eligible for inclusion in this trial the patients must **not** meet any of the following criteria:

1. Any clinically significant medical condition or abnormality, which, in the opinion of the investigator, might compromise the safety of the patient or which might interfere with the trial.
2. Diagnosis of high-risk neuroblastoma (HRNBL) which is currently being treated on the SIOPEN HRNBL trial (patients who have exited this trial will be eligible).
3. Known allergy to 13-CRA or any of the excipients.
4. Inadequate contraception measures in females of childbearing age.
5. Receiving concomitant treatment with tetracyclines.

5.2 Criteria Prior to starting each cycle of 13-CRA

1. Total bilirubin ≤ 1.5 x normal, and (SGPT) ALT ≤ 5 x normal. Veno-occlusive disease if present, should be stable or improving.
2. Skin toxicity no greater than CTCAE Grade 1[10]
3. Serum triglycerides <5.65mmol/L.
4. No haematuria and / or proteinuria on urinalysis.
5. Serum calcium ≥2.0mmol/L to ≤ 2.9mmol/L.
6. Serum creatinine based on age / gender as follows:

Age	Maximum Serum Creatinine µmol/L	
	Male	Female
1 month to < 6 months	35	35
6 months to < 1 year	44	44
1 to < 2 years	53	53
2 to < 6 years	70	70
6 to < 10 years	88	88
10 to < 13 years	106	106
13 to < 16 years	132	124
≥ 16 years	150	124

7. Patients with a seizure disorder must be well controlled and taking anticonvulsants. CNS toxicity < grade 2 (CTCAE).

5.3 Withdrawal criteria

Parent(s)/legal guardian and patients may withdraw from the trial at any time without their care being affected and continue on existing route of 13-CRA administration for remainder of cycles.

1. Positive pregnancy test - pregnancy testing will be undertaken no more than seven days before treatment commences and routinely no more than seven days before each course of treatment in females of childbearing potential. If a patient is found to be pregnant during the trial, the next course of treatment will not be given until the pregnancy has been discussed with the treating clinician, and the patient will be withdrawn from the trial whether or not treatment is continued.
2. Request of the patient, for any reason.
3. Discretion of the investigator.

6 TREATMENT OF PATIENTS

6.1 Evaluation of test and reference treatment

Evaluation of the test and reference product will occur during two months of the therapy only.

Consent to take part in the trial will be obtained before any trial procedures are undertaken. Patients who are already receiving 13-CRA treatment will also be eligible for the trial, so long as they are able to commit to two cycles of trial 13-CRA. The next planned 14-day treatment cycle will be classed as My-CRA Month 1. After consent to take part has been obtained and prior to the initiation of the next 14 day treatment patients will be randomised to receive either13-CRA liquid (test product) or liquid extracted from capsule (reference product) in My-CRA Month 1. Randomisation will be done once eligibility has been confirmed and their next scheduled treatment visit is booked, in order that the appropriate medication can be made available for the

patient's visit. Randomisation will be done centrally by Nova according to a randomisation list generated be the trial statistician, investigators will email (or telephone) Nova to receive randomisation details, this will be confirmed by email as "liquid first" or "extracted capsules first", pharmacy contacts will also be notified. After My-CRA month 1, patients will then cross over to the alternative formulation in My-CRA Month 2. In all other treatment cycles patients will revert to standard therapy i.e. liquid extracted from capsules. The pharmacokinetics of 13-CRA will be evaluated during test and reference treatments (My-CRA Month 1 and 2).

6.2 Permitted medications

Concomitant medication is defined as any medication, other than the trial drug, which is taken during the trial (i.e. before the patient completes the 14 day follow up visit after My-CRA cycle 2), including prescription and over-the-counter medicines.

For the purposes of the trial, nutritional supplements including vitamins and minerals are not considered concomitant medications, although vitamin A supplements will not be allowed (according to standard practice). The generic names of medications should be used where possible. Concomitant medication will be recorded in the CRF with indication, dose information, and dates of administration. Any new medications taken or any changes to the form, frequency or dose of existing medication occurring during the trial will also be recorded. The use of concomitant medications is based upon the experience of the clinical investigator.

6.3 Monitoring compliance

Medication will be prescribed and dispensed by the pharmacy. On pharmacokinetic days (Day 1 and 14) morning doses of medication will be administered in the clinic. All additional doses of medication will be recorded fully on the patient's diary card. Prescription, dispensing and accountability of 13-CRA will be accurately recorded in the drug accountability log provided by the Sponsor. The trial monitor will verify that the data have been accurately recorded and transferred.

6.4 Exit points

The normal exit point from this trial will be when the patient completes the 14 day follow up visit in My-CRA month 2, all adverse events will be followed up to conclusion.

6.5 Expected duration of patient participation

Patients will be in the trial for a 2 month period.

7 INVESTIGATIONAL MEDICINAL PRODUCT

The term 'Investigational Medicinal Product' will refer to the 13-CRA liquid administered to the patient as part of the pharmacokinetic trial.

7.1 Description of investigational medicinal product

Drug Substance	13-Cis Retinoic Acid
Manufacturer of Drug Product	The test drug product will be manufactured and batch released by: Nova Limited, Martin House, Gloucester Crescent, Wigston, Leicester, LE18 4YL. The reference drug product will be an approved, commercial product that will be purchased by the Sponsor and supplied to the local pharmacy, the manufacturer is: Roche Products Limited, 6 Falcon Way, Shire Park, Welwyn Garden City, AL7 1TW. Product License: PL 00031/0160
Test Drug Product	Novel oral liquid formulation of 13-Cis Retinoic Acid
Reference Drug Product	Isotretinoin capsules-Roaccutane® 20 mg soft capsules (to be extracted per dosing instructions provided)
Daily dose	The dose administered will be 200mg/m^2/day for both test and reference product. Patients with a body weight of ≤12kg will receive a dose of 160 mg/m^2.
Frequency	100 mg/m^2 twice daily (morning and evening) for 14 days per patient
Packaging, Test Drug Product	50 ml Amber type III glass bottle with tamper evident child-resistant closure. Packaged with oral dosing syringes. Storage at room temperature (15 to 25^{o}C) The medicinal product is photosensitive and should be protected from light and stored in the original carton at all times Shake the bottle vigorously for at least 30 seconds before use
Packaging, Reference Drug Product	Capsules, soft 10 and 20 mg capsules: Oval, opaque, brown-red and white capsules imprinted with ROA 20 in black ink. Duplex (PVC/PVDC) aluminium blister packs containing 20, 30, 50 or 100 capsules. Storage at room temperature (15 to 25^{o}C)

The product will be prepared and dosing on the pharmacokinetic days will be by the site staff or by parents supervised by site staff, and will be according to instructions provided by The Sponsor (separate document to be version controlled). Remaining doses will be given to the patients by their parents/guardians, and will be according to instructions provided to them. Parents will be trained according to these instructions and local hospital standard procedures.

13-CRA dosing will be prescribed by qualified medical personnel.

7.3 13-CRA dosing

The appropriate dose will be delivered to each patient, according to the weight of the patient to deliver approximately 200 mg/m^2 13-CRA. Patients with a body weight of ≤12kg will receive a dose of 160 mg/m^2.

Each patient enrolled in the trial will receive 13-CRA in accordance with the dosing requirements.

Initial doses will be administered and checked by trained medical/nursing staff and recorded accurately in a controlled drug accountability log provided by the Sponsor. Remaining doses will be recorded by the parents/guardians in the diary card.

The Sponsor monitors will check the accuracy of the pharmacy and site for receipt of IMP, confirmation of receipt, pharmacy storage of the IMP packages, distribution records to the clinic and records of return to pharmacy and destruction of IMP. Any anomalies will be queried and clearly documented. All records will be maintained in the hospital pharmacy files with anonymised copies retained for the Sponsor trial master file.

7.4 Packaging and labelling

The Sponsor will provide sufficient quantities of IMP in accordance with Good Manufacturing Practice (GMP). The clinical trial supplies will be properly packaged and labelled in accordance with applicable local regulatory requirements.

7.5 Preparation, handling and storage

The IMP will be accounted for in a drug inventory and stored in a locked area in the pharmacy or in the hospital clinic until used in the trial. Storage information and batch characteristics will be supplied at the time of delivery. At the end of the trial the site will be contacted about the handling procedures for unused trial drug. The IMP will be destroyed by the site according to local procedures, this will be appropriately documented.

7.6 Investigational medicinal product accountability

The principal investigator at each site is responsible for ensuring the investigational medicinal product (IMP) accountability, including reconciliation of the IMP and maintenance of IMP records.

- Upon receipt of the IMP the principal investigator (or delegated pharmacist) will check for accurate delivery and acknowledge receipt by signing (or initialling) and dating the documentation provided by the supplier and faxing/scanning a copy back to the supplier. The original will be retained in the investigator/pharmacy file.
- The dispensing of the IMP will be carefully recorded on the appropriate drug accountability forms provided by the Sponsor. An accurate account will be made available for verification by the Sponsor monitor at each monitoring visit.
- IMP accountability records will include:
  - Release of the IMP by the supplier's Qualified Person.
  - Confirmation of IMP delivery to the trial site.
  - The inventory at the site of IMP provided by the supplier.
  - Details of pharmacy dispensing.
  - Administration of IMP to patients (in clinic, and on diary cards).
  - Destruction of excess IMP. All unused IMP will be destroyed by pharmacy personnel according to normal hospital policy, destruction will be clearly recorded, documented and checked by The Sponsor monitors.
  - Return to the supplier or alternative disposition of unused IMP.
- The principal investigator should maintain records that adequately document that:
  - Patients were treated with the dose specified in the protocol.
  - Preparation/administration and return/destruction of IMP was properly conducted.

Unused IMP must not be discarded without prior permission from the Sponsor or used for any purpose other than the present trial. IMP that has been dispensed must be accurately recorded for each patient.

The Sponsor monitor will periodically collect the IMP accountability forms and check all IMP data (both used and unused) prior to making arrangements for the return of unused IMP to the supplier or authorising their destruction by the trial site.

8 PREMATURE DISCONTINUATION FROM TRIAL

8.1 Early Discontinuation of an Individual Patient

Patients and their parent(s)/legal guardian will be informed that they have the right to withdraw from the trial at any time, without prejudice to their medical care and that they are not obliged to state their reasons. In addition, the investigator may remove a patient from the trial if, in the investigator's opinion, it is not in the best interest of the patient to continue in the trial.

Any withdrawal from the trial must be fully documented in the CRF and source.

The date of discontinuation from the trial and reason (where possible) for discontinuation will be recorded on the CRF and in the patient's medical records.

- Patients may be discontinued from the trial for the following reasons:
- Withdrawal of consent
- AE
- Deviation from protocol
- Other (to be specified on the CRF by the investigator if possible)

The data recorded (including PK samples) until the time of withdrawal will be used as part of the clinical trial unless the parent(s)/legal guardian or patient requests that it is not used.

Withdrawn patients may be replaced if the overall target number of samples has not been reached (i.e. a total of 150 samples).

8.2 Early Discontinuation of the Trial

If, in the opinion of the investigator, the clinical observations in the trial suggest that it might not be justifiable to continue, he may terminate the trial following consultation with the Sponsor. Alternatively, the Sponsor may give written notification to the investigator, regulatory authorities and ethics committees of the early discontinuation of the trial, including reasons.

In case of early discontinuation of the trial, safety assessments should be performed for each patient, as far as possible.

8.3 Patient and Trial Completion

Patients will be considered to have completed the trial when the patient has completed the 14 day's follow up at the end of the My-CRA Month 2 dosing period. Patients who consent for the trial but who do not, for whatever reason, receive trial medication will be considered to be screening failures and their data will be recorded on a screening failure list. Patients who provide at least one pharmacokinetic blood sample for trial purposes will be deemed to have entered the trial and will be included in the PK analyses. All patients who receive trial medication will be considered for the safety analyses.

The trial will be considered to be completed 14 days after the last patient's has completed their My-CRA Month 2 dosing.

9 ASSESSMENT OF SAFETY

Assessments of safety will be performed throughout the time that the patient is in clinic and for the 14 days that the patient receives medication at home (and for 14 days between dosing cycles

if adverse events are recorded in the diary card or are spontaneously reported by the patient to hospital staff) and 14 days from the time that the patient receives their last dose (Two weeks follow up after Day 14 of the treatment).

The on-going safety of the investigational medicinal product will be assessed through the recording, reporting and clinical assessment of baseline medical conditions, and adverse events recorded until discharged (and for 14 days follow up between cycles or post last dose if recorded in the diary card or spontaneously reported by the patient to hospital staff). Trial site personnel will report any adverse event (AE), whether observed by the research staff or reported by the patient.

Oro-praryngeal tolerability will be assessed at baseline and following dosing until a patient has completed the trial. Any local clinically relevant changes will be recorded as adverse events.

9.1 Definition of adverse events

An AE is any untoward medical occurrence in a patient or clinical trial patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not related to the IMP.

During the trial, any worsening of conditions, signs or symptoms noted from the time of consenting to take part in the trial will be recorded as an AE.

All AEs that occur (whether treatment related or not) will be recorded in the CRF throughout the duration of the visit (and for 14 days post dosing if recorded on the diary card or spontaneously reported to hospital staff).

As far as possible, each AE must be described by its duration (start and end time and date or ongoing), its frequency (single episode, intermittent, continuous), its severity (mild, moderate, severe - see section 9.2), a causality assessment (coexisting disease, concomitant medication, the IMP, or other cause), its relationship to the IMP (unrelated, unlikely, possibly, probably, definitely – see Section 9.2), whether this influenced the course of the IMP, whether it required specific action or therapy, and outcome.

All medical conditions present at baseline should not be considered as AEs unless these have worsened during the trial phase. In cases of surgical or diagnostic procedures the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

9.2 Expected AE in 13-cis-retinoic acid recipients

Refer to Investigator Brochure.

9.3 Adverse events

Using the WHO toxicity criteria as a guide, the principal investigator will assess the severity of all AEs according to the following definitions:

Mild: The patient is aware of the event or symptom but it is easily tolerated.
Moderate: The patient experiences sufficient discomfort to interfere with or reduce his / her usual level of activity
Severe: Significant impairment of functioning – the patient is unable to carry out usual activities and/or the patient's life is at risk from the event.

The principal investigator will assess the relationship of AEs to the investigational medicinal product using the following definitions:

Definite: There is a definite clinical/biological relationship and time sequence between the onset of the AE and the administration of the investigational medicinal product.

Probable: A causal relationship is clinically/biologically highly plausible and there is a plausible time sequence between onset of the AE and administration of the investigational medicinal product and there is a reasonable response on withdrawal.

Possible: A causal relationship is clinically/biologically plausible and there is a plausible time sequence between onset of the AE and administration of IMP.

Unlikely: A causal relationship is improbable and another documented cause of the AE is most plausible.

Unrelated: A causal relationship can be definitively excluded and another documented cause of the AE is most plausible.

In case of a fatality the cause of death is captured as the AE and the death is its outcome.

10 PROCEDURE FOR RECORDING AND REPORTING ADVERSE EVENTS

Adverse event data will be recorded throughout the patient's stay in the clinic/hospital (and for 14 days post dosing if recorded in the diary card or if reported spontaneously to hospital staff).

10.1 Recording of adverse events in the case report form

As quality and precision of AE data collected is of key importance, the principal investigator or his designee should use the AE definitions provided in the above sections and follow the guidelines below when completing the AE pages of the CRF:

- Whenever possible recognised medical terms should be used to describe AEs rather than colloquialisms (e.g. 'influenza' rather than 'flu'). Abbreviations should be avoided. An adverse event term needs to be provided for each adverse event, preferably using the Short Name as listed in the Common Terminology Criteria for Adverse Events version 4 (CTCAE, current version 4.02), available online (10).
- AEs should be described using a specific clinical diagnosis rather than component signs and symptoms where possible (e.g. 'congestive heart failure' rather than 'dyspnoea, rales and cyanosis').
- Signs and symptoms that are considered unrelated to a specific disease or syndrome should be reported as individual AEs on the CRF (e.g. 'nausea' and 'vomiting' should be recorded separately and not as 'nausea and vomiting').
- Provisional diagnoses (e.g. 'suspected asthma') are acceptable but should be followed up by a definite diagnosis when/if finally available.
- AEs that are secondary to other events (e.g. 'sequelae or complications) should be identified by the primary cause. A primary AE, if clearly identifiable, generally represents the most accurate clinical term to be recorded on the AE pages of the CRF. The principal investigator should be invited to provide his/her own opinion of which is the primary AE.

10.2 Reporting of adverse events

Complete and appropriate data on all AEs experienced during the clinical trial will be reported in the AE pages of the CRF on an ongoing basis for the duration of the reporting period.

It is important that each AE report includes a description of the event, its seriousness status and criteria, duration, severity, relationship to the investigational medicinal product, other causality factors (if any), any concomitant medications dispensed, concomitant procedures prescribed or other actions taken and its outcome at the end of the reporting period.

10.3 Serious Adverse Events

A Serious Adverse Event (SAE) is defined as one of the following:

- An event that causes the death of the patient.
- A life-threatening* event.
- An event causing hospitalisation** or prolongation of existing hospitalisation.
- An event causing persistent or significant disability or incapacity.***
- An event causing a congenital anomaly or birth defect in the offspring of a subject treated before or during pregnancy.
- Important medical events (i.e., not immediately life-threatening or do not result in death or hospitalisation but require urgent and intensive intervention to prevent one of the outcomes listed in the definition above, for example, intensive treatment at home or in an emergency room for bronchospasm or convulsion)

* The term 'life-threatening' refers to an event in which the patient was at risk of death at the time of event; it does not refer to an event that hypothetically might have caused death if it were more severe.

** A hospitalisation is defined as an overnight stay, including time spent in an emergency room, for an AE (although subject has to have been admitted to a ward or remained in hospital >24 hours). A prolongation of existing hospitalisation is defined as an additional overnight stay. Elective surgery is not classified as an SAE. For the purposes of this trial, admission for an elective surgical procedure/ routine procedure/ routine assessment will not be considered an SAE unless there is a prolongation to the anticipated duration of hospitalisation for a procedure/assessment of that nature. Any other unanticipated outcome of a procedure/assessment that meets the definition of a serious adverse event should be reported.

*** The term 'persistent or significant disability or incapacity' refers to an event that results in a substantial or permanent disruption of patient's ability to carry out normal life functions.

Pregnancy is not considered to be an adverse event. However if any female becomes pregnant during the course of the trial, she will be followed up to determine the outcome of both the mother and foetus. Also if the partner of a male patient enrolled in the trial becomes pregnant, the mother and foetus will also be followed-up to determine the outcome of both.

10.4 Reporting Serious Adverse Events

All SAEs occurring during the trial or within 7 days following the completion of the trial by the patient must be reported to The Sponsor by fax or email within 24 hours of the investigator becoming aware of the SAE.

SAE EMERGENCY CONTACT DETAILS

Investigators should not wait to receive additional information to fully document the event before notifying the Sponsor of a SAE. A full written summary, detailing relevant aspects of the

SAE, should follow the initial fax report. Where applicable, information from relevant hospital case records and post-mortem reports should be obtained.
Any SAE that is both unexpected and suspected to be related to treatment (SUSAR) must be reported by the Sponsor to the regulatory authorities and the REC (via the investigator) within the following time limits:

- A SUSAR that is fatal or life-threatening is to be reported to the regulatory authorities and the REC as soon as possible, and in any case no later than seven days after the Sponsor first becomes aware of it. Relevant follow-up information must be reported within an additional 8 days.
- All other SUSARs are to be reported to the regulatory authorities and the REC as soon as possible, but within a maximum of 15 days of the Sponsor first becoming aware of it.

10.4.1 Reporting procedures

The Serious Adverse Event Form must be completed as fully as possible with information relevant to the serious adverse event(s) being reported. All fields should be populated or marked accordingly if no information is available. If it is not possible to complete all sections of the Serious Adverse Event Form within 24 hours, transmission of the form must not be delayed and the outstanding information should be sent on a follow-up Serious Adverse Event Form. The investigator must complete the Serious Adverse Event Report Form as fully as possible, assess causal relationship to trial treatment and send the completed form by fax within 24 hours to the Sponsor. In cases of death reported as a serious adverse event, the report should detail the main and contributory causes of death. This information should also be accompanied by a death certificate or autopsy report, if available. The Sponsor will in any case report any death or life-threatening event to the authorities (MHRA and REC) within 7 calendar days, if it is both unexpected and considered to be drug-related, with any follow up reports within a further 8 calendar days. Any other serious adverse event that is both unexpected and considered drug-related will be reported within 15 calendar days. The original and the duplicate copies of the Serious Adverse Event Form, and the fax confirmation sheet must be kept with the case report forms at the trial site. The monitor will collect a copy of the Serious Adverse Event Form and deliver it to the Sponsor. For all serious adverse events where important or relevant information is missing, active follow-up should be undertaken. Investigators or other site personnel should inform Safety contact of any follow-up information on a previously reported serious adverse event. The follow-up information must be presented on a Serious Adverse Event Form marked as follow-up. It is necessary only to provide the new information, with the Serious Adverse Event Form signed by an investigator.
Investigators or other site personnel should send relevant or requested supporting documentation (e.g. electrocardiogram (ECG), laboratory results, autopsy report to Safety contact.)
The investigator will ensure that all the necessary information is provided within the timelines stipulated by Safety contact when the request for information is made.
Follow-up reports should be completed and transmitted following the same procedure as for the initial report. The follow-up should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or discontinued trial participation. The form and fax confirmation sheet must be retained. The Sponsor may also request further follow-up information following review of the Serious Adverse Event Form. The investigator will make all reasonable attempts to obtain the follow-up information requested and forward it to the Sponsor as detailed above. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous termination, details of the birth, and the presence or absence of any congenital abnormalities or birth defects. The investigator will provide these details via completion of a Pregnancy Follow-up form.

11 EVALUATION OF RESULTS

Changes in the conduct of the trial or planned analyses will be reported in the corresponding section of the trial report.

A Statistical Analysis Plan (SAP) will be developed by a qualified statistician together with a pharmacokinetic modeller. Pharmacokinetic and Statistical analysis will be performed according to this document. The SAP will specifically include details of how all: Analysis Populations, Demographic and Baseline Characteristics, Completion and Discontinuation information, Medication details, Pharmacokinetic analyses as well as Safety analyses (including oro-pharyngeal tolerability) and Palatability will be classified and described. The SAP will be reviewed and approved prior to analysis.

The sample size chosen for the trial is considered appropriate based on previous experience. No formal sample size calculations have been performed. In order to develop a robust population pharmacokinetic model (i.e. precisely estimated parameters), data from a minimum of 150 blood samples will be required. It is hoped that the required number of samples may be obtained from 12-18 patients. However, if problems are encountered in obtaining samples further patients may be included in the trial. In order to accommodate these problems without having to submit repeated protocol amendments the protocol states up to 18 patients for inclusion in the trial.

11.1 Pharmacokinetic analysis

Since a sparse sampling approach is to be employed in the present trial it is not possible to use a classical analysis to obtain PK parameter estimates. Therefore, a population-PK approach will be applied. In the population approach all data from different individuals are fitted simultaneously using a non-linear, mixed effects modelling approach and post hoc individual kinetic parameters can be calculated with as few samples as one per individual.

Data will be analysed using the mixed effects non-linear regression modelling programme, NONMEM (version V II; ICON). Post processing of NONMEM output will be undertaken with an appropriate statistical package such as R (current version).

Preliminary analyses will focus on the structural and variance models. One and two compartment models with first and zero order inputs will be implemented. Between patient variability will be assumed to be log-normally distributed, and residual error will be modelled using additive, proportional and combined error structures.

Biologically plausible covariates will be included in the model for analysis e.g. age, weight. A multivariate analysis will be performed, details of this analysis will be included in the SAP. Several criteria can be used to evaluate the improvement in the model performance and thus select the final model. Comparisons of hierarchical models are based on the objective function value, i.e. two times the negative log likelihood value. Changes in the objective function value > 7.88 ($p<0.005$) are accepted as statistically significant. The other selection criteria used include improvement in the goodness of fit and residual plots, increased precision in parameter estimation, and reduced variance of between patient and residual errors. An assessment of model appropriateness will be undertaken using visual predictive checks and posterior predictive checks. This will be based on the final covariate model.

The metabolite 4-oxo-13-cis-retanoic acid will also be evaluated. The absorption function, CL/F, V/F will be considered as primary PK parameters; secondary PK parameters (such as Tmax, Cmax, AUC and half-life) will be calculated from the primary model parameters. .

11.2 Safety, tolerability and palatability analyses

Reporting of the safety data will be of a descriptive nature and presented using appropriate summary statistics (e.g. n, mean, SD, %CV, median, minimum, maximum) or frequency

distributions (n%) by age group (age 1-11 years, age 12-< 21 years). Unless otherwise stated these tabulations will be supported by data listings.

Safety summaries will include all patients irrespective of whether or not they completed the trial.

AEs will be coded according to the current version of MedDRA (version to be identified in trial report).

Treatment emergent adverse events (TEAEs) will be determined and only these will be included in the statistical analysis report. Details of the criteria of classifying an AE as a TEAE will be provided in the Statistical Analysis Plan.

The incidence of adverse events will be summarised by system organ class, preferred term and maximum severity. Adverse events will also be summarised by strongest relationship to Investigational Medicinal Product by event and system organ class. If a patient experiences an adverse event more than once the event with the worst severity or at the most related to IMP occurrence will be considered. Patients will be included only once at each level where they experienced one or more events.

A summary of the incidence of serious adverse events will be presented by event and system organ class.

Adverse events relating to oro-pharyngeal tolerability data will be additionally listed separately and appropriately summarised.

All results for other safety will be appropriately summarised.

Palatability data will be appropriately summarised.

11.3 Data Safety Monitoring Committee (DSMC)

An independent Data Safety Monitoring Committee will be formed to alert and/or make recommendations to The Sponsor about any existing or potential safety issues.

11.4 Reporting urgent safety measures

If any urgent safety measures are taken the Investigator/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures.

Please refer to the following website for details on clinical trials safety reporting: http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Safetyreporting-SUSARSandASRs/index.htm

11.3 Statistical analysis

11.3.1 Analysis Populations

The primary trial population will be the Pharmacokinetic (PK) population. The PK population will include those patients who had at least one successful blood sample taken and complete the trial without significant protocol deviations/violations which are likely to affect the determination of the pharmacokinetic parameters. Further details on what is deemed a significant protocol deviation/violation will be documented in the Statistical Analysis Plan. This population will be used for the analysis of the primary variable.

Safety data will be presented for the Safety population, that is, it will include all patients who received trial medication.

11.3.2 Sample Size

Up to 20 patients, both male and female, aged 0 – < 21 years of age will be recruited.

There are no power calculations in this trial. The objective of this trial is to estimate the population pharmacokinetics of 13-CRA following the administration of 13-CRA liquid (test product) and extracted capsule (reference product). From a statistical point of view, the collected plasma 13-CRA concentration data are expected to relate to a non-linear, mixed effects model involving repeated measures. The developed pharmacokinetic model will estimate the parameters of the model and their associated within- and between-patient variability.

11.3.3 Data Analysis

Statistical analyses will be performed after all patients have ended their participation in the trial, protocol deviations reviewed, populations have been agreed and the database has been locked.

Details of this analysis will be included in the SAP.

Patients withdrawn before treatment administration will not be assessed for outcome variables or safety.

Continuous variables will be summarised using descriptive statistics; n, mean, standard deviation, %CV, median, minimum and maximum, while categorical variables will be summarised as the number (and percentage) of patients in each category.

Baseline and demographic data will be summarised overall and by age group (age 1-11 years, age 12-< 21 years) as appropriate.

Concomitant medications will be tabulated by age group along with the current available WHO drug dictionary coding by primary term and generic drug name.

As part of the pharmacokinetic analysis, statistical significance will be declared at the 5% level (two- sided). All other safety analyses will be simply summarised.

11.3.4 Missing, Unused or Spurious Data

The handling of missing, unused and spurious data will be described in the Statistical Analysis Plan.

11.3.5 Deviations from the Planned Statistical Analyses

Any changes to the planned analysis (as described in the protocol and Statistical Analysis Plan) will be documented in the statistical and clinical trial reports.

12 REGULATORY AND ETHICAL CONSIDERATIONS

12.1 Good Clinical Practice

The investigator and Sponsor will ensure that this trial will be performed in accordance with the protocol, the Declaration of Helsinki (9), and all applicable regulatory requirements. The trial will be conducted according to the protocol and to Standard Operating procedures (SOPs) that meet the guidelines laid down by the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) in clinical trials. The Sponsor has implemented a quality management system to manage quality throughout all stages of the trial process, using a risk-based approach. A Study Management Plan will be developed and will include a risk analysis for identification, evaluation, control, communication, review and reporting of the risks to the safety and integrity of the patients and the scientific integrity of the trial. This risk analysis will identify processes and data that are critical to ensure human subject protection and reliability of results, this risk assessment will be reviewed as appropriate during the study.

12.2 Informed consent

Before a patient can participate in the trial their parent(s)/legal guardian must give written informed consent to participation. Where applicable, the patient themselves will provide assent for the trial (generally in patients over 7 years of age). The informed consent process will be in accordance with ICH GCP, the Declaration of Helsinki and local regulatory requirements.

Patient information leaflets/informed consent forms will be based on master documents provided by the Sponsor and submitted and approved by the Independent Ethical Committee (IEC). Patient information leaflets will be designed to target specific age groups and levels of understanding in order to obtain patient assent for the trial as well as parental/legal guardian consent. The Sponsor must approve and retain copies of any changes requested by the IEC before the documents are used.

12.3 Regulatory authority approval

Before the trial is initiated at a site the Sponsor will obtain approval to conduct the trial from the appropriate regulatory authority in accordance with any applicable country specific requirements. Regulatory authority approval for the clinical trial will be obtained prior to recruitment of patients into the trial and shipment of IMP.

12.4 Independent ethics committee requirements

Before initiation of the trial at a given site written approval of the protocol, informed consent forms and patient information leaflets will be obtained from the appropriate independent ethics committee. If any amendments to any of these documents occur during the trial, written approval must be obtained prior to their implementation. The site will also apply to their Local Authority and IEC as appropriate for approval to participate in the trial. The principal investigator at each site is responsible for ensuring that these actions occur.

12.5 Data Safety Monitoring Committee (DSMC)

Before initiation of the trial the final trial protocol will be supplied to the independent Data Safety Monitoring Committee who will make recommendations to The Sponsor about any existing or potential safety issues.

12.6 Indemnity and Insurance

With respect to any liability directly or indirectly caused by the IMP in connection with this clinical trial the Sponsor assumes liability on behalf of the investigator for possible injury to the patient, provided the investigator has followed the instructions of the Sponsor in accordance with this protocol and any amendments thereto, that the IMP has been supplied by the Sponsor, and that the investigator has performed the clinical trial in accordance with scientific practice and currently acceptable techniques and knowledge. The Sponsor's liability is covered by liability insurance.

12.7 Patient Confidentiality

The principal investigator must ensure that the patient's anonymity is maintained. On the CRFs or other documents submitted to the Sponsor, patients should not be identified by their names, but by their assigned identification number. If patient names are included on copies of documents submitted to the Sponsor, the names must be obliterated and replaced with the assigned trial patient numbers.

The principal investigator should keep a separate log of patient identification numbers, names, addresses, telephone numbers and hospital numbers (if applicable). Documents not for

submission to the Sponsor, such as signed informed consent forms, should be maintained in strict confidence by the principal investigator in the trial site file.

A screening failure log will be maintained for patients who have consented to participate in the trial but who, for whatever reason, are not eligible, withdrawn or decide to withdraw prior to taking part. This log will contain the following information:

- Patient trial number
- Patient initials
- Reason for trial withdrawal (if available)

CRF pages will not be completed for these patients.

The investigator shall permit authorised representatives of the Sponsor, regulatory authorities and IECs to review that portion of the patient's medical record that is directly related to the trial. As part of the required content of informed consent, the patient must be informed that his/her records will be reviewed in this manner. The Sponsor will have access to patients information on site during monitoring or auditing, no identifying information other than patient number will be transferred to the Sponsor.

12.8 Trial Documentation and Storage

The investigator/institution should maintain the trial documents in a comprehensive and centralised filing system that is suitable for inspection by representatives of the Sponsor and regulatory authorities. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents as defined by ICH GCP include the signed protocol and any amendment(s), copies of the completed CRFs, signed informed consent forms from the parent(s)/legal guardians of all patients for whom consent was obtained, hospital records and other source documents, IEC approvals and all related correspondence including approved documents, drug accountability records, site delegation lists and curriculum vitae, trial correspondence and a list of the patients' names and addresses.

The principal investigator must retain copies of all essential documents for the period specified by ICH GCP and by applicable regulatory requirements.

The principal investigator will inform the Sponsor of the storage location of the essential documents and must contact the Sponsor for approval before disposing of any of these documents.

It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained. The Sponsor should be informed immediately by the investigator/institution of any change concerning archiving facilities.

12.9 End of trial

For administrative and safety reporting purposes the end of the trial will be defined as 14 days after the last patient completes treatment in My-CRA Month 2. This provides for a single and conservative definition.

12.10 Publication Policy

The Sponsor will prepare a written clinical trial report according to ICH guidelines to summarise the trial following completion of the analysis.

Investigators may not submit trial information for publication without prior consultation and written approval from the Sponsor. However such approval should not be unreasonably withheld.

13 ADMINISTRATIVE OBLIGATIONS

13.1 Source Data

All relevant trial data will be recorded in the CRF. Where relevant data already exists on other source documents such as laboratory reports or ECGs, the information required will be transcribed into the CRF. All other data will be directly written into the CRF.

13.2 Monitoring

Routine monitoring visits will be made by the monitors designated by the Sponsor to check compliance with the protocol, the completeness, accuracy and consistency of the data, and adherence to GCP.

The principal investigator must ensure that CRFs are completed in a timely manner and must allow periodical access to CRFs, patient records, drug logs and all other trial-related documents and materials. The frequency of monitoring visits will be determined by factors such as trial design and the site enrolment requirements. For this trial, monitoring visits will usually occur a few weeks after a patient is recruited and completes My CRA-Month 2, at an individual site.

The investigator will agree to provide the monitor direct access to the patients' source data, which may exist in the form of hospital records, patient files and notes, and laboratory assessment reports and results.

13.3 Quality Control and Quality Assurance

Appropriately qualified and trained staff will be involved in this trial. Staff at the investigational site will be instructed in the conduct of the trial according to this protocol.

In order to check the compliance of the trial regarding GCP, audits may be carried out by a quality assurance representative. The investigator will provide access to authorised persons during regulatory authority inspections or Sponsor audits.

13.4 Data Collection and Management

A CRF will be completed for each patient who enters the trial. The CRFs will be printed and the original CRFs will be collected by the Sponsor or their delegate – a photocopy will be retained at the site.

The CRFs should be completed legibly in English with a black ball-point pen. Errors should be crossed by a single line but not obliterated, and the change initialled and dated by the investigator or designee. The use of correction fluid or tape is not allowed. The investigator will sign and date at the indicated places in the CRF. This signature will indicate a thorough inspection of the data on the CRF has been made, and will certify the contents of the form.

CRFs will be completed promptly and submitted to the monitor in person for checking and collection. When changes to CRF data are necessary following removal of the original CRF from the trial site these changes will be documented on data clarification/resolution forms which will be signed by the investigator.

The data will be entered into a validated database. TASK Applied Science Pty Ltd will be responsible for data processing, in accordance with the Sponsor or Sponsor's delegated service provider's data management procedures. Database lock will occur once quality assurance procedures have been completed. Nova will send results to other South Africa. Patients information sheets will include details that cover data being sent outside of the UK, and the consent form will cover a request for consent to do so.

Data items from the CRF will be entered centrally into the trial database by Data Management using double data entry, with verification upon second entry. Concomitant medication entered onto the database will be coded using the WHO Drug Reference List. Coexisting diseases and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Laboratory samples will be processed and results sent to Data Management.

13.6 Adherence to the Protocol

Protocol violations are any deviations from the procedures outlined in this document, for example, missed evaluations, incorrect timing of evaluations, non-compliance with IMP and intake of prohibited medications. It is the investigator's responsibility to make all reasonable efforts to avoid protocol violations in order to avoid possible exclusion of the patient from the trial and/or analyses.

All protocol violations will be reported immediately to the Sponsor and any action required, for example, discontinuation of the patient will be discussed. Evaluability of the patient(s) concerned will be performed by the Sponsor prior to the statistical analysis.

Any deviation from the protocol that has not been approved by The Sponsor and the IEC could result in a discontinuation from the trial of the site involved.

13.7 Trial or site discontinuation

The Sponsor may temporarily or permanently discontinue the trial at a single site or at all sites for safety, ethical, compliance or other reasons. If this is necessary, The Sponsor will endeavour to provide advance notification to the site(s) involved. If the site or trial is suspended or discontinued, the principal investigator will be responsible for promptly informing the IEC. Where required by local regulations, The Sponsor will be responsible for informing the IEC of trial or site discontinuation. In such cases, all trial data and unused investigational medicinal product must be returned to The Sponsor.

13.8 PERSONNEL RESPONSIBILITIES

The trial will be conducted in accordance with the protocol, Good Clinical Practice and applicable regulatory requirements.

13.8.1 Investigator

The investigator's responsibilities shall include but not be limited to:

(i) adhering to the conduct of the trial as described in this protocol
(ii) ensuring the accuracy and legibility of the CRFs and their security
(iii) immediately reporting any serious adverse events to the Sponsor and, if appropriate, the Ethics committee
(iv) adhering to the guidelines described in the Declaration of Helsinki and ICH Guideline for Good Clinical Practice and local regulatory requirements.
(v) informing the patient's general practitioner that the patient is taking part in the trial, provided that the patient agrees to this contact. A copy of the correspondence should be filed in the Investigator Site File.
(vi) Provide expert research input and advice relating to trial design and execution.
(vii) Be responsible for the review and sign-off of the final report.

13.8.2 Clinical monitor

The clinical monitor's responsibilities shall include but not be limited to:

(i) verifying protocol adherence
(ii) verifying the data on the CRFs with information in the patient's clinic notes and other source documents

(iii) ensuring the trial documents such as the CRFs, protocol and any correspondence are maintained in a secure area

(iv) reporting and discussing any problems with the investigators and reporting them to the Sponsor.

13.8.3 Sponsor

As trial Sponsor's responsibilities shall include but not be limited to:

(i) providing the principal investigator with all the necessary trial documents and trial supplies prior to trial initiation

(ii) providing the investigator with updates on new developments regarding the trial drug

(iii) sending the principal investigator financial reimbursement during the conduct of the trial according to a schedule agreed upon in the budget

14 REFERENCES

1. Gareth J. Veal, Julie Errington, Sophie E. Rowbotham *et al*. Adaptive dosing approaches to the individualization of 13-cisretinoic acid (isotretinoin) treatment for children with high-risk Neuroblastoma. Clin Cancer Res. 2013 January 15; 19(2): 469–479. doi:10.1158/1078-0432.CCR-12-2225

2. Hewson QD1, Lovat PE, Corazzari M, Catterall JB, Redfern CP. The NF-kappaB pathway mediates fenretinide-induced apoptosis in SH-SY5Y neuroblastoma cells. Apoptosis. 2005 May;10(3):493-8.

3. Reynolds CP, Schindler PF, Jones DM, Gentile JL, Proffitt RT, Einhorn PA. Comparison of 13-cis-retinoic acid to trans-retinoic acid using human neuroblastoma cell lines. Prog Clin Biol Res 1994;385:237–44.

4. Veal GJ, Errington J, Redfern CPF, Pearson ADJ, Boddy AV. Influence of isomerisation on the growth inhibitory effects and cellular activity of 13-cis and all-trans retinoic acid in neuroblastoma cells. Biochem Pharmacol 2002;63:207-15.

5. Khan AA, Villablanca JG, Reynolds CP, Avramis VI. Pharmacokinetic studies of 13-cis-retinoic acid in pediatric patients with neuroblastoma following bone marrow transplantation. Cancer Chemother Pharmacol 1996;39:34-41.

6. Khan AA, Villablanca JG, Reynolds CP, Avramis VI. Pharmacokinetic studies of 13-cis-retinoic acid in pediatric patients with neuroblastoma following bone marrow transplantation. Cancer Chemother Pharmacol 1996;39:34-41.

7. High Risk Neuroblastoma Study 1.7 of SIOP-Europe (SIOPEN), note this is the current protocol (dated as of approval of this My-13 CRA study protocol), when enrolment completes patients will be treated under the next version of this study protocol.

8. Oral retinoids: pregnancy prevention—reminder of measures to minimise teratogenic risk MHRA 25 June 2013. https://www.gov.uk/drug-safety-update/oral-retinoids-pregnancy-prevention-reminder-of-measures-to-minimise-teratogenic-risk

9. Declaration of Helsinki: http://www.wma.net/en/30publications/10policies/b3/

10. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 Published: May 28, 2009 (v4.03: June 14, 2010) available at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Guidance documents:

Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States, Official Journal of the European Communities, 1.5.2001; L 121/34-44.

European Clinical Trials Directive, 2005/28/EC European Good Clinical Practice Directive and associated guidance.

ICH Topic E 6. Guideline for Good Clinical Practice. Step 5, Consolidated Guideline from 01.05.1996. Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95). Jan.1997.

INTEGRATED ADDENDUM TO ICH E6(R1): 1 December 2016 EMA/CHMP/ICH/135/1995
Committee for Human Medicinal Products. Guideline for good clinical practice E6(R2)
Step 5

Statutory Instruments (UK Law): SI 2004 No. 1031, 2006 No 1928. The Medicines For Human Use (Clinical Trials) Regulations 2004 and associated amendments.

EUROPEAN COMMISSION: Guidance Document: Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial (CT-1) (2010/C 82/01)
https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2010_c82_01/2010_c82_01_en.pdf

EUROPEAN COMMISSION: Guidance Document: Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3') (2011/C 172/01)
https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2011_c172_01/2011_c172_01_en.pdf

15 APPENDICES

Appendix I Trial schedule

Appendix II Co-Investigator Signature sheet

Appendix III Protocol Amendments

APPENDIX I TRIAL SCHEDULE: EACH CYCLE

Test	Pre trial	Day 1	Day 14	Day 15/16	End of trial[7] (Day 29)
Informed consent / assent[1]	x				
Medical history	x				
Concomitant medications	x	x	x		x
Physical Examination	x				
Pregnancy Test[2]	x				
Check for central line in situ	x	x			
13-CRA morning dose		x	x		
Pharmacokinetic blood samples[3]		x	x	x	
Vital signs for safety[4]		x	x		
Palatability[5]			x		
Oro-pharyngeal tolerability[6]		x	x		x
Adverse events / serious adverse events[7]		x	x		x

1 Parents/legal guardian will be asked to give informed consent to their child participating in the pharmacokinetic trial before 13-CRA is administered. Patients over the age of 7 years will be asked to give their assent to participate in the pharmacokinetic trial if it is deemed appropriate.
2 Pregnancy test for females of childbearing age, not more than 7 days prior to starting treatment (each cycle).
3 Up to five pharmacokinetic blood samples will be taken.
4 Systolic and diastolic blood pressure, pulse and body temperature at baseline (in older patients this will be following 5 mins rest in supine position).
5 Palatability assessment will be made at the 14 day visit. This will be done using a face to face survey.
6 Assessed at baseline and during the trial and follow up
7 On discharge from site or withdrawal from trial (AEs followed for up to 14 days later, if in diary card or if reported to research staff.

APPENDIX II CO-INVESTIGATOR SIGNATURE SHEET

INVESTIGATOR SIGNATURE SHEET

The signature below constitutes approval of this protocol by the signatory and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol including all statements regarding confidentiality.

I have read this protocol and agree that it contains all necessary details for carrying out this trial. I will conduct the trial as outlined herein and in accordance with the ethical principles of the Declaration of Helsinki and ICH GCP guidelines. I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this trial. I will discuss the material with them to ensure they are fully informed regarding the drug and the conduct of the trial.
I will only use the informed consent form approved by the sponsor or its representative and will fulfill all responsibilities for submitting pertinent information to the Independent Ethics Committee (IEC) responsible for the trial.

INVESTIGATOR

NAME: (to be completed for each investigator)

ADDRESS: (to be completed for each investigator)

Signed: _____

Date: _____

APPENDIX III PROTOCOL AMENDMENTS

PROTOCOL AMENDMENT NUMBER 1 (Version 1.0 to Version 2.0):

Reason for Amendment - 1: Administrative amendment
Removal of named pharmacovigilance provider as QPPV was interim, general contact details at PV Service provider listed here, the named individual will be identified in the trial master file (correspondence)

Changed reference to "children" to "patient" throughout to reflect the patient population age up to 21 years.

Page 1:

*The following text is to be **deleted**:*

VERSION NUMBER: 1.0

DATE: 30 March 2017

*The following text is to be **added**:*

VERSION NUMBER: 2.0

DATE: 9 June 2017

Page 3:

*The following text is to be **deleted**:*

[redacted]

*The following text is to be **added**:*

[redacted]

PROTOCOL AMENDMENT NUMBER 2 (Version 2.0 to Version 3.0):

Reason for Amendment - 2: Administrative amendment

Update to include requirements of ICH E6R2, quality management, risk-based approach and definition of critical data.

A requirement to remove the requirement for patients to be high-risk Neuroblastoma, as some patients with intermediate risk may be eligible.

Section 3.5 to clarify that oncology history may be diagnosis only and treatment only needs to include treatment in the last month.

Section 4.6 clarification of food to be given with food and the removal of standardised meals

Small administrative edits.

Page 1:

*The following text is to be **deleted**:*

VERSION NUMBER: 2.0

DATE: 9 June 2017

*The following text is to be **added**:*

VERSION NUMBER: 3.0

DATE: 28 Sept 2017

Page 19:

*The following text in italics is to be **added**:*

- Oncology history *(diagnosis)* and treatment *(over the last month)* to include concomitant medication for their indication (i.e. confirmation of eligibility for 13-CRA treatment and current treatment).

Page 21:

*The following text is to be **deleted**:*

appropriate standardised meals/drinks to be provided to patients during the period following dosing on PK days

*The following text in italics is to be **added**:*

which foods such as yogurt or ice cream can be given with the medicine

Page 35:

*The following text in italics is to be **added**:*
The Sponsor has implemented a quality management system to manage quality throughout all stages of the trial process, using a risk-based approach. A Study Management Plan will be developed and will include a risk analysis for identification, evaluation, control, communication, review and reporting of the risks to the safety and integrity of the patients and the scientific integrity of the trial. This risk analysis will identify processes and data that are critical to ensure human subject protection and reliability of results, this risk assessment will be reviewed as appropriate during the study.

Page 44:

An error on the study schedule was corrected (medical history and concomitant medications to be collected at pre-trial visit) adverse events also added as to be collected on PK days).

PROTOCOL AMENDMENT NUMBER 3 (Version 3.0 to Version 4.0):

Reason for Amendment - 2: Administrative amendment, inconsistencies in blood sampling schedules

Change in flow chart to remove pre-dosing blood sample as was intended, i.e. to reduce the number of samples taken from each child.

Small administrative edits.

Page 1:

*The following text is to be **deleted**:*

VERSION NUMBER: 3.0

DATE: 28 Sept 2017

*The following text is to be **added**:*

VERSION NUMBER: 4.0

DATE: 11 Oct 2017

Page 12:
*The following Text will be **deleted:***
A pre-dose blood sample will be taken (2ml) and then blood will be sampled post-dose at time points selected as follows:
Page 12:
*The following Text will be **added:***
Blood (2 ml) will be sampled post-dose at time points selected as follows:

Page 21:

*The following text is to be **deleted**:*

On Days 1 and 14 an initial blood sample will taken (pre-dose, at time zero).

PROTOCOL AMENDMENT NUMBER 3 (Version 4.0 to Version 5.0):

Reason for Amendment - 3: Requirement from MHRA to include explicit timelines for pregnancy testing and addition of a lower limit of serum calcium prior to initiation of each cycle of 13-CRA.

Clarification of Name of Sponsor to be correct.

Addition of light protection and shaking requirements for test product.

Throughout document:

Nova *Biopharma* Limited will be replaced with Nova *Laboratories* Limited

Page 1:

*The following text is to be **deleted**:*

VERSION NUMBER: 4.0

DATE: 11 Oct 2017

*The following text is to be **added**:*

VERSION NUMBER: 5.0

DATE: 08 Dec 2017

Page 10, Synopsis, Inclusion criteria 5:
*The text **in underlined italics** will be **added:***

5. Negative pregnancy test for females of child-bearing potential *no more than seven days* before initiation of treatment, and sexually active patients and partners agreeing to undertake adequate contraceptive measures (see section 4.5).

Page 11, Synopsis, Criteria prior to starting each cycle of 13-Cis-RA 5:
*The text **in underlined italics** will be **added:***

5. *Serum calcium ≥ 2.0mmol/L to ≤ 2.9mmol/L.*

Page 11, Synopsis, Withdrawal criteria 1:
*The text **in underlined italics** will be **added:***

1. Positive pregnancy test - pregnancy testing will be undertaken *no more than seven days* before treatment commences and routinely *no more than seven days* before each course of treatment in females of childbearing potential. If a patient is found to be pregnant during the trial, the next course of treatment will not be given until the pregnancy has been discussed with the treating clinician, and the patient will be withdrawn from the trial whether or not treatment is continued.

Page 21, Pregnancy prevention, Paragraph 1:
*The text **in underlined italics** will be **added:***
For women of childbearing potential all conditions of the Pregnancy Prevention Programme should be met (8). Patients of childbearing potential, their partners and parents must understand and accept the need for effective contraception, be informed and understand the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy. Female patients of childbearing age must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if appropriate. As part of the standard clinical care, female patients of childbearing potential will undergo a pregnancy test *no more than seven days* prior to the start of treatment and routinely no more than seven days before each course of treatment. Although the likelihood of pregnancy in patients receiving 13-CRA is extremely low, if a positive pregnancy test does result during the trial, the next course of treatment will not be given until the pregnancy has been discussed with the treating clinician, and the patient will be withdrawn from the trial whether or not treatment is continued

Page 23, Section 5 Selection of Patients; Section 5.1, Inclusion criteria 5:
*The text **in underlined italics** will be **added:***

5. Negative pregnancy test for females of child-bearing potential *no more than seven days* before initiation of treatment, and sexually active patients and partners agreeing to undertake adequate contraceptive measures (see section 4.5).

Page 11, Section 5 Selection of Patients; Section 5.2, Criteria prior to starting each cycle of 13-Cis-RA 5:
*The text **in underlined italics** will be **added:***

5. Serum calcium *≥ 2.0 mmol/L to* ≤ 2.9mmol/L.

Page 11, Section 5 Selection of Patients; Section 5.2, Withdrawal criteria 1:
*The text **in underlined italics** will be **added:***

1. Positive pregnancy test - pregnancy testing will be undertaken *no more than seven days* before treatment commences and routinely *no more than seven days* before each course of treatment in females of childbearing potential. If a patient is found to be pregnant during the trial, the next course of treatment will not be given until the pregnancy has been discussed with the treating clinician, and the patient will be withdrawn from the trial whether or not treatment is continued.

Page 26, Investigational Medicinal product, Packaging, Test Drug Product:
*The following text is to be **added**:*
The medicinal product is photosensitive and should be protected from light and stored in the original carton at all times
Shake the bottle vigorously for at least 30 seconds before use

Page 44, Appendix 1 Pregnancy testing Footnote 2:
*The text **in underlined italics** will be **added:***
2. Pregnancy test for females of childbearing age, *not more than 7 days* prior to starting treatment (each cycle).