Contract

OECD 488 transgenic rodent mutation assay (TGRA) using the Big Blue® rat

UNIVERSITY OF SHEFFIELD

F03: Contract award notice
Notice identifier: 2022/S 000-014913
Procurement identifier (OCID): ocds-h6vhtk-032075
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Section I: Contracting authority

I.1) Name and addresses

UNIVERSITY OF SHEFFIELD

Western Bank

SHEFFIELD

S102TN

Contact

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Country

United Kingdom

NUTS code

UKE32 - Sheffield

Internet address(es)

Main address

https://www.sheffield.ac.uk

I.4) Type of the contracting authority

Body governed by public law

I.5) Main activity

Education

Section II: Object

II.1) Scope of the procurement

II.1.1) Title

OECD 488 transgenic rodent mutation assay (TGRA) using the Big Blue® rat

II.1.2) Main CPV code

- 73111000 - Research laboratory services

II.1.3) Type of contract

Services

II.1.4) Short description

The conduct of an OECD 488 transgenic rodent mutation assay (TGRA) using the Big Blue® rat using cII mutant selection for the University of Sheffield. Studies will be conducted to GLP, and are based on the following preliminary study design:

1. Breeding of target cohort of 46 Big Blue male rats, with delivery of a target of 44 rats to

Charles River Laboratories (CRL) facility, Ashland Ohio, USA.

2. Transfer of HPLC analytical method for dose formulation analysis (DFA) and method transfer summary performed by CRL.

3. Method validation, homogeneity, solubility and stability work to enable GLP dose formulation analysis during Big Blue® TGRA main study, performed by CRL.

4. 7-day dose-range finding study (DRF), wild type Fischer F344 male and female rats, to determine limit dose of 1000 mg / kg body weight /day or MTD, performed by CRL.

5. Big Blue® TGRA rat main study, male only, using vehicle, 3 dose groups and concurrent positive control conducted at CRL. Each group will contain at least 6 male rats, conducted in accordance with OECD 488; daily test item administration by oral gavage for 28 days (positive control will be dosed days 1, 3, 10, 17 & 24 only); termination and schedule necropsy on day 31 with duodenum, liver and bone marrow removed from all animals, flash frozen and stored prior to shipment to Gentronix.

6. Pig-A in vivo mutation analysis will be integrated into the Big Blue® TGRA study, with all study animals screened for elevated Pig-A locus mutation in the pre-study acclimatisation phase, and then a blood sample taken from all animals on study on day 31 as a terminal bleed to minimise animal handling procedures and impact onto the Big Blue® TGRA study. Pig-A analysis will be performed by CRL, unless Sheffield advises of an alternative third party analysis partner, consistent with GLP study principles.

7. Dose formulation analysis during conduct of the main study, performed by CRL.

8. Analysis of liver and duodenum (bone marrow will not be analysed initially) from 5 animals per dose group in the in vitro phase of the Big Blue® TGRA study as per OECD 488 will be conducted at and performed by Gentronix. DNA will be extracted, packaged into lambda bacteriophage used to infect E. coli strain G1250 to determine phage packaging efficiency and cII mutation detection after plating on agar. Phage packaging titres of at least 125,000 per animal will be determined, to facilitate estimation of mutation frequency.

9. GLP reporting of results.

II.1.6) Information about lots

This contract is divided into lots: No

II.1.7) Total value of the procurement (excluding VAT)

Value excluding VAT: £366,300

II.2) Description

II.2.3) Place of performance

NUTS codes

- UKD62 - Cheshire East

Main site or place of performance

The majority of the work will be performed in Alderley Edge, Cheshire with c33% of the work (in-life) sub-contracted to Charles River Laboratories in Ohio, USA.

II.2.4) Description of the procurement

In August 2021 the University of Sheffield entered into a contract with WuXi AppTec (Hong Kong) Ltd (Find A Tender Service Contract Award Notice Publication Reference: 2021/S 000-021618) for the provision of IND enabling toxicology study services for M102 (small-molecule drug candidate; oral route, once daily), including 2 animal studies.

It is now the intention of the University of Sheffield to contract the third animal study (Big Blue) to Gentronix Limited. Studies will be conducted to GLP, and are based on the following preliminary study design:

The conduct of an OECD 488 transgenic rodent mutation assay (TGRA) using the Big Blue® rat using cII mutant selection for the University of Sheffield. Studies will be conducted to GLP, and are based on the following preliminary study design:

1. Breeding of target cohort of 46 Big Blue male rats, with delivery of a target of 44 rats to Charles River Laboratories (CRL) facility, Ashland Ohio, USA.

2. Transfer of HPLC analytical method for dose formulation analysis (DFA) and method transfer summary performed by CRL.

3. Method validation, homogeneity, solubility and stability work to enable GLP dose formulation analysis during Big Blue® TGRA main study, performed by CRL.

4. 7-day dose-range finding study (DRF), wild type Fischer F344 male and female rats, to determine limit dose of 1000 mg / kg body weight /day or MTD, performed by CRL.

5. Big Blue® TGRA rat main study, male only, using vehicle, 3 dose groups and concurrent positive control conducted at CRL. Each group will contain at least 6 male rats, conducted in accordance with OECD 488; daily test item administration by oral gavage for 28 days (positive control will be dosed days 1, 3, 10, 17 & 24 only); termination and schedule necropsy on day 31 with duodenum, liver and bone marrow removed from all

animals, flash frozen and stored prior to shipment to Gentronix.

6. Pig-A in vivo mutation analysis will be integrated into the Big Blue® TGRA study, with all study animals screened for elevated Pig-A locus mutation in the pre-study acclimatisation phase, and then a blood sample taken from all animals on study on day 31 as a terminal bleed to minimise animal handling procedures and impact onto the Big Blue® TGRA study. Pig-A analysis will be performed by CRL, unless Sheffield advises of an alternative third party analysis partner, consistent with GLP study principles.

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9. GLP reporting of results.

Schedule - subject to CRL timelines and Study Plan

• In-life study phases commence at CRL in either December 2022 (if dose range finding study required) or January 2023 (if main phase OECD 488 study only)

• In-life study phases complete at CRL in February 2023

• Post-life in vitro phases commence at Gentronix Limited in February 2023

• Post-life in vitro phases complete at Gentronix Limited in April 2023

• Draft report - by end May 2023

Gentronix's Limited's choice of partnership with CRL was based on 4 main factors:

1. They are a significant contract research organisation, high animal welfare standards and with capabilities at their Ashland facilities to conduct all necessary aspects of the in-life Big Blue studies. These include supporting toxicological and analytical endpoints and in particular they have coverage for all expected routes of exposure/administration including via inhalation;

2. The laboratory team at Ashland has previous experience of acting as GLP main test site and Study Director for Big Blue® studies, commissioned by the previous asset owner

being BioReliance Corporation. This substantially de-risks the GLP compliance elements of these studies, and was viewed favourably in our discussions with the UK MHRA prior to commencing work on this project;

3. The USA location and relative close proximity to our animal facility breeding location in NY. This enables ground transportation of animals within a timeframe that provides no compromise on animal welfare and shipments are routine from our contract breeder to these facilities;

4. In many circumstances they were and are an established service provider to the same clients Gentronix Limited receives enquiries from for Big Blue® studies. This de-risks commercial, contractual and legal discussions.

At present the CRL Ashland facility is the only site capable of conducting GLP compliant in-life subcontract work for Big Blue studies on behalf of Gentronix.

II.2.5) Award criteria

Price

II.2.11) Information about options

Options: No

Section IV. Procedure

IV.1) Description

IV.1.1) Type of procedure

Award of a contract without prior publication of a call for competition in the cases listed below

- The services can be provided only by a particular economic operator for the following reason:
    - absence of competition for technical reasons

Explanation:

Negotiated procedure without prior publication

32. (2) (b) (ii) - The works, supplies of services can be provided only by a particular economic operator for the following reason:

o Competition is absent for technical reasons

Explanation

BigBlue test and MutaMouse test are both qualified genotoxicity studies using transgenic rodent models to enable the US FDA investigational new drug (IND) filing and the initiation of first-in-human studies. BigBlue assay uses transgenic rats, while MutaMouse assay uses transgenic mice.

To identify the rodent and non-rodent species relevant to human, the research teams at UoS and its partners (including Aclipse) have conducted a metabolite identification study. Potential metabolites of M102 were identified and possible metabolic pathways were predicted in liver microsomes from various species (mouse, rat, dog, monkey, human). It was observed that the metabolites in human liver microsomes were relevant to those of rats and monkey. As a result, rat and monkey were selected as appropriate rodent and non-rodent species for toxicological evaluations for M102. In fact, the non-GLP M102 general toxicological study in rats has already been performed which makes the BigBlue assay the next scientifically logical step. The use of BigBlue assay (i.e., transgenic rat model) to evaluate the in vivo genotoxicity of M102 can be well justified.

Gentronix Limited have proprietary ownership of the Big Blue genetically specific breeding colony and methodology, meaning that there are no other CLP compliant providers who can provide this assay.

A single source is therefore proposed to formalise the solution provided by Gentronix Limited for the following reasonss that it has proprietary ownership of the Big Blue® Transgenic Rodent (TGR) Gene Mutation Assay which is stipulated in order to obtain FDA approval.

The Services to be delivered will commence around December 2022, are due to take 6 months and complete by May 2023

IV.1.8) Information about the Government Procurement Agreement (GPA)

The procurement is covered by the Government Procurement Agreement: Yes

IV.2) Administrative information

IV.2.1) Previous publication concerning this procedure

Notice number: 2022/S 000-006619

Section V. Award of contract

A contract/lot is awarded: Yes

V.2) Award of contract

V.2.1) Date of conclusion of the contract

13 May 2022

V.2.2) Information about tenders

Number of tenders received: 1

The contract has been awarded to a group of economic operators: No

V.2.3) Name and address of the contractor

Gentronix Limited

Cheshire

Country

United Kingdom

NUTS code

- UKD62 - Cheshire East

The contractor is an SME

Yes

V.2.4) Information on value of contract/lot (excluding VAT)

Total value of the contract/lot: £366,300

V.2.5) Information about subcontracting

The contract is likely to be subcontracted

Section VI. Complementary information

VI.4) Procedures for review

VI.4.1) Review body

High Court of England, Wales and Northern Ireland

London

Country

United Kingdom