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CANCER RESEARCH UK

Centre for Drug Development

Clinical Study Protocol

A Cancer Research UK Phase I study of MOv18 IgE, a first in class chimeric IgE antibody against folate receptor-α, in patients with advanced solid tumours

Protocol number: CRUKD/14/001

EudraCT number: 2014-000070-19

Version: 13.0

Date: 29 April 2021

Chief Investigator: Prof James Spicer

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Chief Scientific Investigator: Dr Sophia N. Karagiannis

[redacted]

Sponsor: Cancer Research UK
Centre for Drug Development

[redacted]

PARTICIPATING INVESTIGATORS AND CENTRES:

Details of Principal Investigators and Investigational Sites are recorded on the Participating Investigators and Centres list in the Sponsor's Trial Master File.

PROTOCOL VERSION HISTORY:

Version No.	Version Date	Reason for update
1.0	17 September 2014	Initial version submitted to MHRA and then withdrawn prior to formal response following comments from MHRA Expert Advisory Group.
2.0	17 December 2014	CTA re-submission to MHRA and initial submission to REC.
3.0	22 January 2015	Response to GNA submission to MHRA. Exclusion of bisphosphonates (MHRA request)
4.0	03 December 2015	Minor amendment to Appendix 8.
5.0	23 February 2017	Change from intradermal to skin prick testing, refinement of criteria for dose-limiting toxicity and associated changes
6.0	19 October 2017	• Clarification of additional samples to be taken in response to positive skin prick tests and infusion reactions • Medications to be available at bedside • Skin prick test training • [redacted] • Updates to Appendix 4: Treatment of Anaphylaxis.
7.0	19 December 2017	• Anaphylaxis no longer a DLT but considered a 'dose independent significant toxicity' (added as a primary endpoint). • Assessment of anaphylaxis – frequency to be considered across whole study. Assessment triggered by Grade 2 events. • Update to trial specific grading of anaphylaxis. • Add positive basophil activation test (BAT) as an exclusion criterion • Revise timepoints for skin prick response assessment
8.0	08 August 2018	• Grade 4 Fatigue has been removed from the DLT criteria • A positive skin prick test is no longer considered to be a 'medically important event'. This is now an 'event of interest' • Wording clarifications and consistencies • Clarification regarding the Trial Steering Group (TSG) and their involvement. • Updates as per new Sponsor protocol template version.
9.0	14 January 2019	• Removal of an eligibility implication of FRα expression in the 'Optional' pre-treatment tumour biopsy. Eligibility is reliant on archival sample result only. • Clarification of wording in Section 7.2.5 relating to additional samples which need to be taken following infusion reactions/anaphylaxis.

Version No.	Version Date	Reason for update
		• Corrections made to Schedule of Events and Blood Volumes • Clarification of wheal diameters measured in Skin Prick Test assessment. • Other minor non-substantial changes and corrections.
10	13 September 2019	• Changes to mandate the paired pre-treatment and on treatment PD biopsies. • Addition of optional skin punch biopsies in the event of Urticaria (any grade) – to be completed for research purposes only. • [redacted] • Wording added to allow additional PK timepoints if emerging data suggested that this would be beneficial. • [redacted] • Addition of (+/-5 mins) window for Drug administration by infusion • Additional clarification and updates to wording in Section 7.2.5 relating to additional samples which need to be taken following infusion reactions/anaphylaxis. • Updates to the PK/PD Assessments methodology • Other minor non-substantial changes and corrections
11	07 January 2020	• [redacted] • Removal of requirement for 28 day and 70 day follow-up PK samples. • Addition of (+/- 4 hr) window for pre-dose bloods. • Updated 60-minute drug admin infusion window to (+/-10 mins) and 90 minute drug admin infusion window (+/-15 mins). • Clarification regarding patient evaluability, should their infusion be interrupted. • Extension of window during which the on-treatment tumour biopsy can be conducted. • Change of Sponsor Address • Other minor non-substantial changes and corrections
12	03 December 2020	• Addition to allow the possibility of Intra-patient dose escalation from Cohort 7 onwards. • Primary prophylaxis (premedication) will be allowed prior to the first infusion of MOv18 IgE based on emerging safety information. • Longer infusion times may be allowed in order to better manage infusion related cutaneous toxicity

Version No.	Version Date	Reason for update
		• Correction to timepoints for clinical laboratory tests in Table 7 • Other minor non-substantial changes and corrections
13	29 April 2021	• Update to include a 1 week washout period following the 1st and 2nd dose of any COVID-19 Vaccination and prior to infusion with MOv18 IgE • Other non-substantial change (correction)

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List of Tables and Figures

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

	Abbreviation	Definition
A	ABPI	Association of the British Pharmaceutical Industry
	ADA	anti-drug antibody
	ADCC	antibody-dependent cell-mediated cytotoxicity
	ADCP	antibody dependent cellular phagocytosis
	AE	adverse event
	alk phos	alkaline phosphatase
	ALT	alanine aminotransferase
	ANC	absolute neutrophil count
	APTT	activated partial thromboplastin time
	AST	aspartate aminotransferase
	AUC	area under the curve
B	BAD	biologically active dose
	BAT	basophil activation test
	BDU	Biotherapeutics Development Unit
	BP	blood pressure
C	CA125	cancer antigen-125
	CD23	low affinity FcεRII
	CDD	Centre for Drug Development
	CI	Chief Investigator
	CLT	total body clearance
	C_{max}	maximum observed plasma concentration
	CR	complete response
	CRA	Clinical Research Associate
	eCRF	electronic case report form
	CSM	Clinical Study Manager
	CT	computerised tomography
	CTA	clinical trial authorisation
	CTCAE	Common Terminology Criteria for Adverse Events version 4.02
	CVA	cerebrovascular accident
D	DLT	dose limiting toxicity
E	ECG	Electrocardiogram
	eCRF	electronic case report form
	EDC	electronic data capture
	ELISA	enzyme-linked immunosorbent assay
F	FACS	fluorescence-activated cell sorting
	FcεR	Fc-epsilon receptor - high-affinity receptor for the Fc region of immunoglobulin E
	FcγR	Fc-gamma receptor
	FR	folate receptor
	FRα	alpha-folate receptor (also known as folate binding protein, LK26 trophoblastic antigen and GP38)
G	GCP	Good Clinical Practice
	GINA	Global Initiative for Asthma
	GMP	Good Manufacturing Practice
H	HAMA	human anti-mouse antibodies
	Hb	haemoglobin
	HCG	human chorionic gonadotropin
	HIV	human immunodeficiency virus

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

	Abbreviation	Definition
I	ICH GCP	International Conference on Harmonisation of Good Clinical Practice
	IgE	Immunoglobulin E
	IgG	Immunoglobulin G
	IHC	immunohistochemistry
	IL (IL-)	interleukin
	IMP	investigational medicinal product
	INR	international normalised ratio
	ITF	Investigator Trial File
	IV	Intravenous
K	Ka	affinity constant
	Kd	elimination rate constant
M	MAOI	monoamine oxidase inhibitor
	MIA	manufacturing authorisation holder
	MHRA	Medicines and Healthcare products Regulatory Agency
	MOv18	chimeric IgE monoclonal antibody specific for the alpha-folate receptor
	MRI	magnetic resonance imaging
	MSD	meso scale discovery (assay)
	MTD	maximum tolerated dose
N	NCI	National Cancer Institute
	NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
P	PBMC	peripheral blood mononuclear cell
	PD	pharmacodynamic or progressive disease
	PI	Principal Investigator
	PK	pharmacokinetic
	PR	partial response
	PSRB	Protocol and Safety Review Board
Q	QP	Qualified Person
R	REC	Research Ethics Committee
	RECIST	Response Evaluation Criteria in Solid Tumours version 1.1
	rMOv18	rat MOv18 analogue
	RP2D	recommended Phase II dose
S	SAE	serious adverse event
	SCID	severe combined immunodeficiency
	SD	stable disease
	SOP	standard operating procedure
	SUSAR	suspected unexpected serious adverse (drug) reaction
T	$T_{1/2}$	terminal elimination half-life
	TAMs	tumour associated macrophages
	T_{max}	time to reach C_{max}
	TNFα	tumour necrosis factor alpha
	TSG	Trial Steering Group
U	ULN	upper limit of normal
	USM	urgent safety measure
W	WAG	Wistar Albino Glaxo (a rat strain)
	WHO	World Health Organisation

PROTOCOL SIGNATURES

Investigator Signature:

I have read and agree to the protocol, as detailed in this document. I am aware of my responsibilities as an Investigator under the UK Clinical Trials Regulations[1], the guidelines of Good Clinical Practice (GCP)[2], the Declaration of Helsinki[3] (Appendix 2), the applicable regulations of the relevant NHS Trusts and the trial protocol. I agree to conduct the study according to these regulations and guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study, and ensure that all staff members are aware of their clinical study responsibilities.

Investigator's Name: _____

Name of site: _____

Signature: _____

Date: _____

1 The Medicines for Human Use (Clinical Trials) Regulations (S.I. 2004/1031) and any subsequent amendments to it.

2 ICH Harmonised Tripartite Guideline E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) Step 5, adopted by CPMP July 1996.

3 WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and all subsequent amendments including Oct 2013.

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SPONSOR SIGNATURE

The Sponsor has read and agrees to the protocol, as detailed in this document. I am aware of my responsibilities as the Sponsor under the UK Clinical Trials Regulations[1], the guidelines of Good Clinical Practice (GCP)[2], the Declaration of Helsinki[3] (Appendix 2), the applicable regulations of UK law and the trial protocol. The Sponsor agrees to conduct the trial according to these regulations and guidelines and to appropriately direct and assist sponsor's staff who will be involved in the trial, and ensure that all staff members are aware of their clinical trial responsibilities.

Name: _____

Title: _____

Signature: _____

Date: _____

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1 PROTOCOL SYNOPSIS

Study title: A Cancer Research UK Phase I study of MOv18 IgE, a first in class chimeric IgE antibody against folate receptor-α, in patients with advanced solid tumours.

Short title: Phase I study of MOv18 IgE.

Study Objectives and Endpoints:

Primary Objectives	**Endpoints**
To assess the safety and tolerability of MOv18 IgE	• AEs and DLTs • Dose-independent significant toxicity (Section 3.3.2) • SAEs • Laboratory parameters AEs, SAEs and laboratory abnormalities will be graded according to NCI-CTCAE Version 4.02. Causality of AEs/SAEs will be assessed by the investigator. Infusion-related events will be categorised as due to IgE-mediated mast cell degranulation (anaphylaxis) or cytokine release syndrome.
Secondary Objectives	**Endpoints**
To determine a recommended dose for Phase II evaluation.	The recommended phase II dose (RP2D) will be based on safety data (the Maximum Tolerated Dose; see definition in Section 3.4), and/or efficacy data (the dose at which evidence of anti-tumour activity is seen), and/or pharmacodynamic data, or will be the maximum evaluated dose (50 mg).
To document possible anti-tumour activity in patients treated at doses likely to be pharmacologically active	Best response (according to RECIST 1.1) in patients receiving at least one dose of MOv18 IgE CA125 response in patients with elevated CA125 at baseline
To describe the pharmacokinetics of MOv18 IgE	Serum concentrations of MOv18 IgE
Tertiary Objectives	**Endpoints**
[redacted]	[redacted]

Study design: This is a multi-centre, first in human, Phase I, open label, dose escalation study. Approximately 25 evaluable patients with advanced, unresectable solid tumours expressing the FRα for which no alternative therapy is felt to be appropriate will be entered into this study.

Study treatment: MOv18 IgE will be administered as an IV infusion. Patients in all cohorts will receive a total of six doses of MOv18 IgE at 1-week intervals over a 6 week 'Initial Treatment Period'.

Should additional drug supply become available during the study (for example if dose escalation does not proceed through all the planned dose levels), patients in any cohort who appear to be benefitting from MOv18 IgE may be given up to three further doses of MOv18 IgE at fortnightly intervals called the 'Maintenance Period'. The maximum number of doses for patients, i.e. those completing the 'Initial Treatment Period' and the 'Maintenance Period', would be 9 doses over a total treatment period of 12 weeks.

It is planned that all patients will receive a flat dose of MOv18 IgE without adjustment for body weight or surface area. The starting dose will be 70 µg and dose escalation will be carried out through defined dose levels up to a maximum dose of 50 mg (see Section 5.4 Dose Escalation Scheme). However, a switch to weight-based dosing, and/or intra-patient escalation will be considered during the course of the trial, if emerging data suggest that this could be beneficial, for example by reducing any large inter-patient variations in PK.

2 INTRODUCTION

2.1 Background

Therapeutic antibodies have significantly improved the prognosis of patients with a range of malignancies. Currently available therapeutic antibodies belong to the IgG class, the most prevalent antibody class in human blood. IgE antibodies are known to exert natural immune surveillance in tissues and are engaged locally by the high-affinity IgE receptor, FcεRI, which is present on effector cells such as mast cells, macrophages, basophils and, possibly, eosinophils. IgE antibodies may trigger a more powerful immune response to tumour cells than IgGs, resulting in better anti-tumour efficacy.

MOv18 IgE is a chimeric IgE monoclonal antibody specific for the alpha-folate receptor (FRα), which is expressed on the cell surface of a range of tumour types.

2.2 Investigational medicinal product

2.2.1 Structure of MOv18 IgE

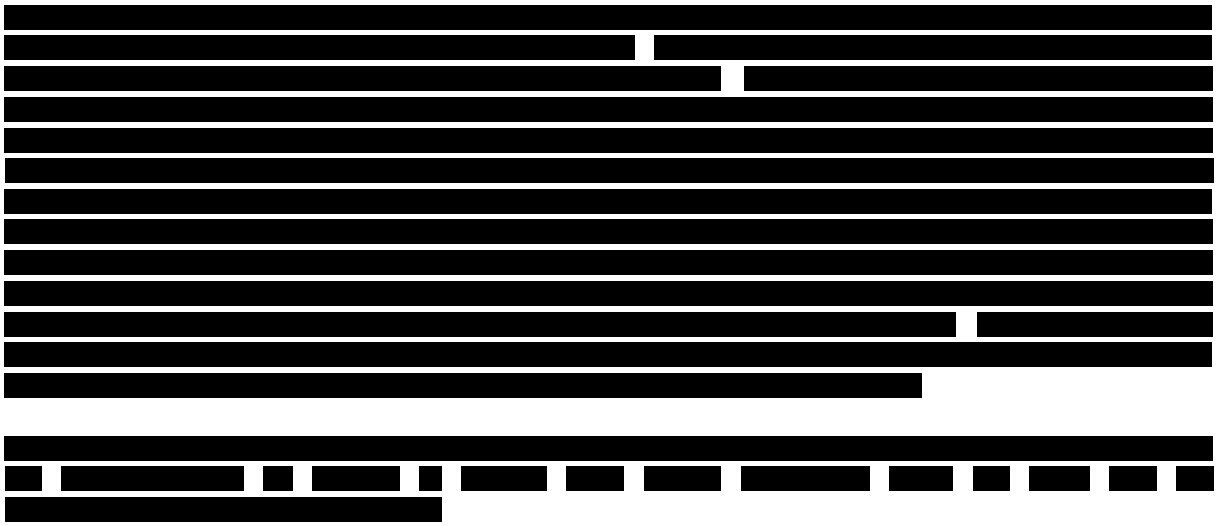


Figure 1: [redacted]

2.2.2 Mechanism of action of MOv18 IgE

All antibody therapies for cancer approved to date have been IgGs (mainly IgG1) (Reichert et al., 2007). However, IgE antibodies have distinct characteristics that may make them an attractive alternative to IgGs for the treatment of malignant diseases:

- IgE has a very high affinity (K_a approximately 10^{10} M^{-1}) for its effector cell receptor (FcεRI). This is 2 to 5 orders of magnitude greater than the affinity of IgG1 for its effector cell receptors (FcγRI, II and III). Once formed, the IgE-FcεRI complex on the effector cell is very persistent owing to the slow dissociation rate of the complex (half-life around 16 hours (h) in cell suspensions). The restricted diffusion of disassociated IgE in tissues also aids reassociation with the receptor and results in a half-life of approximately two weeks in human tissues (Helm et al., 1988).

- As a result of the long lived IgE-FcεRI complex, effector cells are effectively permanently sensitised by IgE when they migrate into tissues. When binding to multimeric antigen occurs, the cell surface IgE-FcεRI complexes become cross-linked and this leads to the release of histamine, enzymes and cytokines. These act to increase circulation to the tissues and lead to an influx and activation of inflammatory and, potentially, cytotoxic cells to the site of allergen provocation. Thus, therapeutic administration of IgE could confer passive immunity against tumours.

- Unlike IgG, there are no known inhibitory IgE Fc receptors

These qualities of IgE result in very different pharmacology to that of the IgG1:

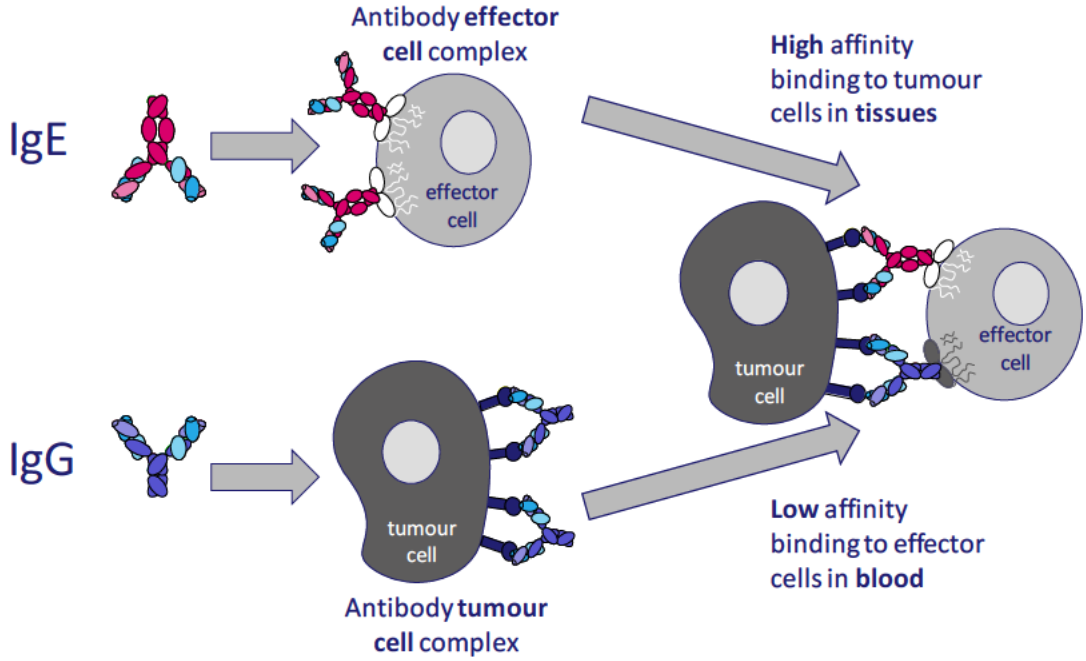
- IgG1 is present at relatively high concentrations in plasma and functions by specifically binding to target antigen followed by relatively inefficient recruitment of effector cells to the antigen-antibody complex via non-antigen specific binding to the Fcγ receptors.

- IgE is present at low concentrations in plasma compared to IgG1 and has variable affinity antigen binding but generally higher affinity effector cell receptor binding. Effector cells initially bind IgE in the blood via non-antigen specific binding to the high affinity FcεRI. IgE is then carried into the tissues by effector cells, and it is the antibody-effector cell complex that specifically binds to the target antigen as part of local immune surveillance (Cheng et al., 2013). Blood IgE concentrations are maintained by B cells carrying excess IgE via the low affinity

FcεRII (CD23) (Cheng et al., 2010). Interaction between IgE and CD23 may also have a role in the phagocytosis of target cells by effector cells, as seen in the IgE-mediated clearance of parasites.

The unique characteristics of IgE and its effector cell-mediated responses may improve the immunotherapy of solid tumours compared with conventional IgG1 therapies. Due to the predominant localisation of IgE antibodies in tissues when bound to their effector cells and the physiological tissue immune surveillance properties of IgE class antibodies, IgEs are appropriately placed to activate tissue-resident effector cells (Jensen-Jarolim et al., 2008). The potency of IgE-dependent cell-mediated cytotoxicity in tissues may lead to efficacy superior to that of IgG1 in solid tumours in cancer patients (Figure 2).

Figure 2: IgE versus IgG



2.2.3 Folate receptor in Human Cancer

MOv18 IgE, like its MOv18 IgG counterpart, specifically binds the FRα (also known as folate binding protein, LK26 trophoblastic antigen and GP38). FRα over-expression has been reported in up to 100% of epithelial ovarian cancers (Kalli et al., 2008; O'Shannessy et al., 2011; Toffoli et al., 1997) and to a lesser extent in carcinomas of the kidney, endometrium, lung, breast, bladder, colon and pancreas (Cagle et al., 2013; D'Angelica et al., 2011; Parker et al., 2005; Ross et al., 1994). In contrast, its expression is limited in normal tissue, where it is restricted to the luminal surfaces of epithelial cells and is not exposed to the bloodstream (Parker et al., 2005; Weitman et al., 1992). FRα over-expression correlates with disease stage and grade and is a marker of more aggressive disease (D'Angelica et al., 2011; Kalli et al., 2008; Toffoli et al., 1997). In addition, over-expression of FRα enhances the growth of tumourgenic cancer cells in vitro and in vivo (Bottero et al., 1993).

2.2.4 Non-clinical efficacy

The affinity of MOv18 IgE for its target antigen has been demonstrated to be similar to that of the chimeric MOv18 IgG1 from which it was derived. This is as intended, resulting in an IgE antibody with target binding similar to MOv18 IgG1, an antibody that has been evaluated in human clinical studies. The affinity of the MOv18 IgE antibody for the FcεRI effector cell receptor has also been established as being typical for an IgE. Using both human blood-derived monocytes and a monocyte cell line, MOv18 IgE was found to produce antigen-specific effector cell-mediated killing of tumour cells expressing FRα, by both antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody dependent cellular

phagocytosis (ADCP). ADCC appears to have been mediated by the high affinity FcεRI, and ADCP by the lower affinity FcεRII (CD23) (Coney et al., 1994; Gould et al., 1999).

In vivo efficacy studies have been performed in two mouse models of ovarian cancer, one using the IGROV1 cell line in SCID mice and one using a HUA ascites cells (a xenograft model of ovarian cancer was established from human primary tumour cells, produced from ascites from a patient with Stage III ovarian carcinoma – these are termed HUA cells) passaged in nude mice. In both models anti-tumour efficacy was observed when MOv18 IgE (at 100 µg/mouse) was co-administered with human peripheral blood mononuclear cells (PBMCs); this efficacy was statistically significantly greater that that after administration of PBMCs alone or after co-administration of PBMCs and MOv18 IgE IgG1. In the HUA model the anti-tumour activity of MOv18 IgE could be abolished by depleting PBMCs of monocytes, and recovered by adding monocytes back to the depleted PBMCs. Co-administration of MOv18 IgE and a monocyte cell line in the HUA model also demonstrated anti-tumour efficacy, and this could be enhanced by stimulation of CD23 expression on the monocyte cell line using IL4. The in vitro anti-tumour activity of MOv18 IgE could therefore be replicated in vivo (Gould et al., 1999; Karagiannis et al., 2008; Karagiannis et al., 2007; Karagiannis et al., 2003).

The in vivo studies in mouse required administration of both human target and human effector cells. This limited the duration of efficacy studies and prevented involvement of the host immune system (since mouse effector cells and human IgE Fc do not interact). Further in vivo efficacy studies were therefore performed in a syngeneic rat model using a surrogate rat MOv18 IgE (rMOv18 IgE). Using a fortnightly dosing schedule, anti-tumour efficacy was observed at rMOv18 IgE doses of 5 mg/kg or greater (but not at lower doses including 1 and 3 mg/kg). After a fortnightly dose of 5 mg/kg the anti-tumour efficacies of rMOv18 IgE and rMOv18 IgG2b were similar, while at 10 mg/kg the IgE was statistically significantly more efficacious. With a weekly administration schedule, a dose of 3 mg/kg rMOv18 IgE demonstrated efficacy that was statistically significantly greater than the same dose of rMOv18 IgG2b. The in vivo anti-tumour efficacy of rMOv18 IgE was therefore maintained in an immunocompetent model (Josephs D et al, manuscript in preparation).

The anti-tumour efficacy of rMOv18 IgE in the rat model was associated with increased tumour necrosis and infiltration of tumour associated macrophages (TAMs). The IgE-associated macrophages had a distinct phenotype that was neither M1 (predominantly expressing killer phenotype) or M2 (involved in tissue repair). The TAMs in rats administered rMOv18 IgE were found to express high levels of intracellular TNFα and IL-10, and high levels of these cytokines were also found in bronchoalveolar lavage together with increased levels of the chemokine MCP-1 and the cytokine IL-1α. The association between these chemo/cytokines and rMOv18 IgE activity is not unique to the rat model. Similarly, elevated levels of MCP-1, IL-10 and TNFα were associated with target cell cytotoxicity in cell killing assays using MOv18 IgE, IGROV1 target cells, and human monocytes. Individual blockade of the action of these cytokines all reduced the cytotoxicity induced by the IgE to some extent (Josephs D et al, manuscript in preparation).

MCP-1 is a chemokine produced by tumour cells and may be responsible for the chemotaxis of monocytes, mast cells and CD8+ T cells into the tumour (Negus et al., 1998; Soucek et al., 2007). IL-1α is a pro-inflammatory cytokine generated by macrophages on inflammatory stimulus. It induces the expression of pro-inflammatory genes in diverse stromal/inflammatory cells, which ultimately act to propagate and sustain inflammation. Taken together, these studies suggest that both rMOv18 IgE and MOv18 IgE may be able to produce anti-tumour efficacy by recruiting macrophages to the tumour, and promoting these TAMs to adopt an IgE-associated phenotype distinct from both the M1 and M2 phenotypes. These IgE induced phenotype TAMs then appear to promote the release of pro-inflammatory cytokines and recruitment of further immune cells to the tumour (Josephs D et al, manuscript in preparation).

In the context of the very high affinity of IgE for its FcεRI (approximately 1 x 10^{-11} M), the mg/kg doses of rMOv18 IgE required for anti-tumour efficacy initially appear higher than might be expected. An efficacious dose of 5 mg/kg rMOv18 IgE is estimated to produce a plasma level of approximately 1 x 10^{-7}M, which is four orders of magnitude greater than the antibody's affinity for FcεRI. The doses required for efficacy of MOv18 IgE in mouse models are also estimated to produce plasma levels of the same order of magnitude. This unexpected finding is thought to be due to competition between exogenously administered IgE and endogenous IgE for binding to effector cell FcεRI in the vascular compartment.

Free IgE is released into the vascular compartment where it binds effector cells and then enters the extravascular compartment bound to FcεRI. This binding step is essential for IgE to reach its target antigens in tissues. Therapeutic MOv18 IgE must compete with endogenous IgE which is already present at steady state levels of around 5 x 10^{-9}M. Administration of MOv18 IgE at doses producing levels of 5 x 10^{-11}M would therefore be outcompeted by the 100 fold higher concentration of endogenous IgE for binding to effector cells. In the absence of effector cell binding MOv18 IgE will not be carried into tissues and may not be expected to have anti-tumour efficacy at these low doses (Josephs D et al, manuscript in preparation).

In both mouse and rat model systems the dose of rMOv18 IgE required for efficacy was adequate to produce concentrations of intravascular IgE significantly greater than endogenous IgE levels for several days post-administration. Such doses would be expected to produce significant tissue levels of rMOv18 IgE-bound effector cells throughout this period.

2.2.5 Non-clinical pharmacokinetics

IgE is present at much lower concentrations and is turned over much more rapidly in blood than IgG. However, IgE in blood is extensively and stably bound to effector cells via FcεRI before entering the extravascular compartment as part of normal immunosurveillance. As a result, the plasma pharmacokinetics of IgE are of limited relevance to the activity of the antibody and are independent of antigen binding. As distribution is largely a consequence of non-selective binding to effector cell FcεRI, the pharmacokinetics of IgE in blood should therefore be independent of the antigen target, with all IgEs competing equally for effector cell binding (Waldmann et al., 1969; Waldmann et al., 1975).

Published data suggest that the half-life of serum IgE in man is 1 to 2 days (Dreskin et al., 1987; Iio et al., 1978) and in rodents approximately 12 hours (Hirano et al., 1983; Vieira et al., 1988). In two separate studies using different detection methods, the half-life of rMOv18 IgE was found to be between 6 and 36 hours. However, the study indicating a longer half-life involved the use of indium-111 radiolabelled antibody, with pharmacokinetics calculated using total radioactivity rather than rMOv18 IgE itself (which could result in an over-estimate of half-life). Therefore, based on existing data on the pharmacokinetics of IgE in rodents and the discussion above, the half-life of rMOv18 IgE in rat serum is estimated to be approximately 12 hours.

[redacted]

Accordingly the clinical trial starting dose and dose escalation plan have been based around competition between the administered MOv18 IgE and endogenous IgE, rather than FcεRI occupancy in an isolated system lacking such competition for binding (see Section 5.1).

2.2.6 Non-clinical toxicology

[redacted]

[redacted]

[redacted]

For additional information concerning MOv18 IgE, refer to the Investigator Brochure.

2.3 Clinical experience

2.3.1 Clinical trials using antibodies and antibody derivatives targeting the folate receptor

This is the first clinical study of a therapeutic IgE antibody targeting the FRα in patients with cancer. However, trials have been conducted using IgGs directed against the FRα, including trials of 'naked' and/or radiolabelled mouse and chimeric IgG versions of MOv18. A humanised version of MOv18 IgG does not appear to have been evaluated in humans, although another humanised IgG targeting the FRα (farletuzumab) is currently in phase III. Overall, MOv18 IgGs and related agents targeting the FRα have been well tolerated in these studies with few side effects reported other than mild-moderate infusion-related events (such as nausea, vomiting, headache, chills, flu'-like symptoms, arthralgia and myalgia) in some patients.

2.3.2 Mouse MOv18 IgG

Two clinical studies involving the administration of mouse MOv18 IgG have been published, both involving radiolabelled antibody. In the first study, a single dose of 0.25 to 1.2 mg mouse [^{131}I]-MOv18 was administered intravenously (n = 20) or intraperitoneally (n = 10) to patients with ovarian carcinoma. A higher tumour uptake and a better tumour/background ratio was seen following intraperitoneal (IP) administration than after IV injection (Crippa et al., 1991). In a subsequent study, 16 ovarian cancer patients with minimal residual disease were administered 8 to 21 mg of mouse [^{131}I]-MOv18 by IP injection (Crippa et al., 1995). Five patients achieved a complete response, six patients no change and five patients had disease progression. In both studies, radiolabelled antibody was well tolerated, apart from mild transient bone marrow suppression attributable to the radioisotope. However, 15 of the 16 patients in the second study (94%) developed human anti-mouse antibodies (HAMA).

Mouse MOv18 IgG1 has also been evaluated as a potential diagnostic and/or therapeutic radiopharmaceutical agent as part of a staged process using biotinylated MOv18 IgG. In the first study, 15 patients with ovarian carcinoma were injected intraperitoneally with 2 mg of biotinylated mouse MOv18 IgG1, followed 3-5 days later by 100-150 µg of indium-111 streptavidin in 500 mL of normal saline (Paganelli et al., 1992). Tumours were imaged 2 to 48 h after the radioactive streptavidin administration and then patients underwent surgery 1 to 8 days later. Results of the trial suggested that this two-step strategy might be superior to the conventional approach (radiolabelled antibodies) for intraperitoneal radioimmunolocalization and radioimmunotherapy of ovarian cancer. No toxicity was observed.

In a subsequent study, a three-step approach was used. Four patients with metastatic ovarian cancer were administered 2 mg of biotinylated MOv18 IgG by intravenous injection (first step), followed

36 hours later by a double injection of 2 mg of avidin (chase) plus 5 mg streptavidin (second step), followed 24 hours later by a third injection of ^{111}In-labeled biotin (third step) (Casalini et al., 1997). The majority of tumours were successfully imaged by immunoscintigraphy following this stage, but the tumour-to-background ratio was relatively low. Toxicity (if it occurred) was not reported. In another study using the three-step approach, 30 patients with ovarian cancer underwent surgery 3 to 4 days after immunoscintigraphy (Magnani et al., 2000). In this study 1 mg of biotinylated MOv18 IgG1 was administered intravenously, followed 24 to 36 hours later with 2 mg of avidin, 5 mg of streptavidin 15 minutes later and then, 24 hours later, by an injection of indium-111 labelled biotin. The presence of tumour in the area of immunoscintigraphic uptake was evaluated in the biopsied material. Twenty-one patients studied were true-positive, five were true-negative, four were false-positive and none was false-negative. On the basis of these data, the authors considered immunoscintigraphy based on MOv18 to be a potentially cost-effective procedure for following up patients after surgery for ovarian carcinoma, since it could potentially identify patients who do not require surgical re-exploration, and guide biopsies when they are indicated. No toxicity was seen in this study although two of the 15 patients tested (13%) developed HAMA.

In the most recent publication on this technique, 38 advanced ovarian cancer patients were treated therapeutically with a three-step protocol (on a compassionate basis). Biotinylated MOv18 IgG (first step) and avidin (second step) were injected intraperitoneally, and 12-18 h later ^{90}Y-labeled biotin was injected either intravenously or intraperitoneally (third step) (Grana et al., 2004). Both regimens (IP, and IP/IV) were well tolerated and no acute side effects were observed although two patients (5%) experienced temporary Grade 3-4 haematological toxicity. In the intraperitoneal group, 6% of patients had objective tumour reduction and 31% had stable disease. In the combined treatment group, 9% of patients achieved objective responses and 32% had stable disease.

2.3.3 Chimeric MOv18 IgG

A single IV infusion of increasing doses of chimeric MOv18 IgG was evaluated in 15 ovarian carcinoma patients (Molthoff et al., 1997). Administration of chimeric MOv18 IgG was described as uneventful with no significant changes in haematological, biochemical, or urine profiles noted at any time following injection. At doses of 50 mg or more, however, all patients experienced infusion-associated side effects such as fever, headache, and nausea/vomiting (Grade 1-2 on the World Health Organization Toxicity Scale). In a subsequent study, five ovarian cancer patients received weekly IV injections (50 mg) for 4 weeks (van Zanten-Przybysz et al., 2002). Administration was described as well tolerated and uneventful in all patients, although infusion-associated Grade 1 nausea, vomiting, headache, chills, flu'-like symptoms, arthralgia and myalgia were reported. Three patients achieved stable disease for up to 4 months, 9 months and 14 months, respectively. Immunological effects of treatment were evaluated in this study but only minor changes were noted (increased antibody-dependent cell-mediated cytotoxicity [ADCC] associated with an increase in CD4+ and CD8+ fractions).

The use of radiolabelled MOv18 IgG1 as a radiotherapeutic agent has also been evaluated. In 24 patients with ovarian cancer the distribution of 1 mg of iodine radiolabelled MOv18 IgG was compared with that of the labelled IgG F(ab')2 fragments (Buist et al., 1993). In a separate study, iodine-131 radiolabelled MOv18 IgG1 was administered to eight patients intraperitoneally at doses of equivalent to 15, 20, 50 or 80 mg or intravenously to four patients at doses of 30, 50 or 75 mg (Buijs et al., 1998). Three patients with ovarian cancer were also administered 10 mg of iodine-131 radiolabelled chimeric MOv18 IgG (van Zanten-Przybysz et al., 2000). The dosimetry of iodine radiolabelled MOv18 IgG1 administered via the IP or IV route has also been examined. Fifteen patients with recurrent epithelial ovarian cancer received a total of 2 to 3 mg of iodine radiolabelled MOv18 IgG1 by a mixture of IP and IV injections (van Zanten-Przybysz et al., 2001). No toxicity attributable to FRα targeting was reported in any of these studies.

No human anti-chimeric antibodies were detected in these studies.

2.3.4 Farletuzumab

Farletuzumab (MORAb-003), a humanised IgG antibody directed against the FR has been evaluated in the phase III setting. In a phase I study in platinum-resistant epithelial ovarian carcinoma, farletuzumab was well tolerated at doses ranging from 12 mg/m^2 to 40 mg/m^2 (Konner et al., 2010). No treatment-

related serious adverse events (SAEs) occurred and no dose-limiting toxicity (DLT) was encountered. The most common treatment-related adverse events were hypersensitivity reactions (15 patients; 60%), fatigue (12 patients; 48%), and diarrhoea (4 patients; 16%). There were no clinically significant changes in cardiac, pulmonary or renal function and no evidence of human anti-human antibody formation. The most common hypersensitivity reactions were pyrexia and chills, which were mostly Grade 1 in severity and occurred during the first infusion. Pharmacokinetic analysis demonstrated a half-life of 5-11 days, consistent with other humanized monoclonal IgG antibodies (this finding was supported by a subsequent population PK analysis (Farrell et al., 2012). Anti-tumour activity was also seen, with four patients achieving a response according to CA125 tumour markers, and seven patients achieving stable disease on imaging. There were no objective responses but nine patients (36%) had stable disease and four patients had a CA125 reduction.

Preliminary data have been published from a phase II study of farletuzumab, conducted in patients with platinum-sensitive epithelial ovarian cancer after an initial remission period of 6-18 months (Armstrong et al., 2008). Twenty-eight asymptomatic patients were given single agent farletuzumab at a dose of 100 mg/m^2 until progressive disease occurred. After nine weeks of treatment, one patient showed a measured reduction in CA125 tumour marker by >75% and a further patient by >25%. Eight patients had stable disease and five patients remained on study for 15-25 weeks. Patients with symptomatic relapse were given standard chemotherapy with carboplatin and paclitaxel combined with farletuzumab. In total, results from forty-one patients were evaluated and amongst these patients, CA125 resolved to normal levels in thirty-seven patients. Six patients remained in remission for longer than their first remission. Although independent radiological reviews were not complete, a 70% response rate was seen. The drug combination was well tolerated, although with infrequent mild infusion reactions noted. Grade 3 toxicity was reported for single agent treatment (headache and abdominal disease secondary to progressive disease), and for farletuzumab in combination with chemotherapy (diarrhoea and neutropenia).

In December 2011, in a company press release, Morphotek, a subsidiary of Eisai Inc., announced the termination of FAR122 (NIH Clinical Trials identifier NCT00738699), a Phase III study of farletuzumab in platinum-resistant ovarian cancer. This decision was based on the results of an interim analysis indicating the study was unlikely to meet its statistically defined endpoints of progression-free survival and overall survival. Safety issues did not play a part in this decision. In January 2013, the company announced that a second phase III trial of farletuzumab (NCT00849667), in platinum-sensitive ovarian cancer, had failed to achieve its primary objective (improved progression-free survival). Overall, these phase I/II/III data suggest that farletuzumab has, at best, modest efficacy in patients with ovarian cancer. However, farletuzumab is well tolerated and adverse effects reported to date do not appear to be related to targeting of the FR in normal tissues.

2.3.5 Other approaches

Other therapeutic approaches targeting the FR include folate-targeted liposomes e.g. (Watanabe et al., 2012), folate-targeted nanoparticles and other novel delivery methods e.g. (Wang et al., 2012), bispecific antibodies (Canevari et al., 1995; Luiten et al., 1997), immunoconjugates of single chain antibodies (Melani et al., 1998), adoptive T-cell therapy using genetically modified T-cells expressing a chimeric anti-FR single-chain antibody (Kershaw et al., 2006), and dendritic cell vaccines transfected with mRNA encoding FR (Hernando et al., 2007).

Vintafolide, a conjugate of folic acid (the ligand for FR) and a vinca alkaloid is in clinical development for ovarian, lung and triple-negative breast cancer. In a phase I study, constipation, nausea, fatigue, and vomiting were the most commonly reported adverse events and constipation was dose-limiting (Lorusso et al., 2012). One partial response to therapy was observed in a patient with metastatic ovarian cancer. A subsequent randomised phase II study of vintafolide in combination with pegylated liposomal doxorubicin (the PRECEDENT study) showed a significant improvement in progression-free survival in patients with platinum-resistant ovarian cancer (Naumann et al., 2010) and this was the basis of an initial EU recommendation for conditional approval. However, an interim analysis of a confirmatory Phase III trial in platinum-resistant ovarian cancer (NIH Clinical Trials identifier NCT01170650; PROCEED trial) was negative and the application for conditional approval was withdrawn. However, evidence of anti-tumour activity has also been reported in a randomised phase II trial of vintafolide in FR-positive adenocarcinoma of the lung (Edelman et al., 2012). Importantly, in relation to the MOv18

IgE CRUKD/14/001 study, the adverse events reported to date for vintafolide do not suggest that toxicities are due to targeting of FR in normal tissues (consistent with clinical data for MOv18 IgG and farletuzumab).

For additional information concerning MOv18 IgE, refer to the Investigator's Brochure.

2.4 Rationale for the clinical study

2.4.1 Rationale for using IgE therapeutically

Monoclonal antibodies directed against tumour antigens have become an important treatment modality in the clinical management of both haematological and solid malignancies in the last 25 years. Several antibodies are now licensed and these humanised or chimeric antibodies behave in a manner similar to naturally occurring immunoglobulins (Reichert et al., 2007). All therapeutic antibodies licensed to date have been IgG antibodies (mainly IgG1). Although they have been shown to be efficacious in the clinical management of some cancers it is possible that other antibody classes - namely IgE - may have superior anti-tumour efficacy because of differences in tissue retention, higher receptor affinity, natural tissue surveillance activities, as well as activation and recruitment of a different spectrum of immune effector and inflammatory cells to the tumour site.

IgE antibodies are primarily known for their role in the immediate hypersensitivity reactions – the basis of conditions such as allergic rhinitis and asthma. IgE antibodies against allergens remain permanently bound to IgE receptors on the surface of IgE receptor-expressing cells such as mast cells, basophils and Langerhans cells. The cross-linking of FcεRI on mast cells by allergen, leads to the release of histamine and cytokines which increases circulation to the tissue and the influx and activation of inflammatory and potentially cytotoxic cells at the site of allergen provocation. These activated cells may also migrate to local lymph nodes to stimulate T cells which in turn migrate to the tissue (Gould et al., 2003). Overall, nonclinical data suggest that the efficacy of immunotherapy for solid tumours may be improved by the use of IgE antibodies in place of the conventional IgG. Nonclinical data and ex vivo data using clinical samples also indicate that MOv18 IgE will not trigger anaphylaxis when administered intravenously to humans, regardless of the presence of FRα-expressing tumours, circulating FRα or FRα-expressing cells.

2.4.2 Rationale for folate receptor alpha as a target

MOv18 IgE is a chimeric antibody raised against an epitope of the human FRα. The significance of this receptor as a tumour marker was discovered in 1991 when amino acid sequence analysis of a protein enriched on the surface of a human ovarian carcinoma cell line showed it to be FRα (Coney et al., 1991). Monoclonal antibodies that recognise FRα revealed that it was expressed on the majority of non-mucinous ovarian carcinomas. However, little to no reactivity was detected on non-epithelial tumours and normal tissues (Miotti et al., 1987). Subsequent publications have reported elevated FRα expression in up to 100% of ovarian carcinomas and lower but elevated expression levels in subsets of other cancers, including endometrial, kidney, lung, mesothelioma, breast, brain, and myeloid leukaemia (Franklin et al., 1994; Garin-Chesa et al., 1993; Holm et al., 1995; Holm et al., 1997; Holm et al., 1994; Parker et al., 2005; Ross et al., 1994; Weitman et al., 1992). Using the immunohistochemical technique planned for this study FRα overexpression is expected to be detectable in around 30-40% of ovarian and endometrial cancers, with less frequent expression in other tumour types (Lawson et al., 2010). The presence of elevated circulating concentrations of FRα has additionally been correlated with biologically more aggressive ovarian cancers (O'Shannessy et al., 2013; Toffoli et al., 1998).

A few normal tissues have been found to express FRα, although most express the protein at lower levels than that detected in FRα-positive carcinomas. Significant FRα expression has been reported in the proximal tubules of the kidney (luminal surface), the choroid plexus, intestinal brush-border membranes, type 1 and type 2 pneumocytes of the lung and placental tissue (Antony et al., 1981; Birn et al., 1997; Birn et al., 1993; Holm et al., 1991; Morshed et al., 1997; Zimmerman, 1990). Expression of FRα in these tissues is generally not accessible to circulating antibodies and so FRα is effectively a tumour-specific antigen.

In clinical trials to date, FRα has been targeted with IgG antibodies. These antibodies have been well tolerated with no evidence of toxicity secondary to FRα binding in normal tissues. However, anti-tumour efficacy has been disappointing. [redacted]

This study will be a proof of principle study, primarily demonstrating the safety of an alternative antibody class in cancer immunotherapy.

3 STUDY DESIGN

3.1 Study objectives and endpoints

Primary Objectives	Endpoints
To assess the safety and tolerability of MOv18 IgE	• AEs and DLTs • Dose-independent significant toxicity (Section 3.3.2) • SAEs • Laboratory parameters AEs, SAEs and laboratory abnormalities will be graded according to NCI-CTCAE Version 4.02. Causality of AEs/SAEs will be assessed by the investigator. Infusion-related events will be categorised as due to IgE-mediated mast cell degranulation (anaphylaxis) or cytokine release syndrome.
Secondary Objectives	**Endpoints**
To determine a recommended dose for Phase II evaluation	The recommended phase II dose (RP2D) will be based on safety data (the Maximum Tolerated Dose [MTD]); see definition in Section 3.4), and/or efficacy data (the dose at which evidence of anti-tumour activity is seen), and/or pharmacodynamic data, or will be the maximum evaluated dose (50 mg).
To document possible anti-tumour activity in patients treated at doses likely to be pharmacologically active	Best response (according to RECIST 1.1) in patients receiving at least one dose of MOv18 IgE CA125 response in patients with elevated CA125 at baseline
To describe the pharmacokinetics of MOv18 IgE	Serum concentrations of MOv18 IgE
Tertiary Objectives	**Endpoints**
[redacted]	[redacted]

3.2 Design of the Study

This is a multi-centre, first in human, Phase I, open label, dose escalation study. Approximately 25 evaluable patients with advanced, unresectable solid tumours expressing the FRα will be entered into this study. The final number will depend on: the number of dose escalations required to reach DLT, or

to reach a threshold frequency of dose-independent significant toxicity (Section 3.3.2) or to reach the maximum planned dose level (50 mg).

It is expected that the study will take about 4 to 5 years depending upon the number of cohorts explored during dose escalation.

MOv18 IgE will be administered as an IV infusion. Patients in all cohorts will receive a total of six doses of MOv18 IgE at 1-week intervals (over an initial dosing period of 6 weeks). This dosing period, called the 'Initial Treatment Period', is considered a loading phase. During this period, three weeks of treatment is considered one cycle.

Should additional drug supply become available during the study (for example if dose escalation does not proceed through all the planned dose levels), patients in any cohort who appear to be benefitting from MOv18 IgE may be given up to three further doses of MOv18 IgE at fortnightly intervals, starting two weeks after the sixth dose of MOv18 IgE, and continuing at the same dose level as the last dose received. This additional period is considered a maintenance phase. The total number of doses for patients completing the 'Initial Treatment Period' and the 'Maintenance Period' would be 9 over a treatment period of 12 weeks.

Please refer to Figure 3: MOv18 IgE Dosing Schedule in Section 5.3.

It is planned that all patients will receive a flat dose of MOv18 IgE, without adjustment for body weight or surface area. The starting dose will be 70 µg and dose escalation will be carried out through defined dose levels up to a maximum dose of 50 mg (see Section 5.4 Dose Escalation Scheme). However, a switch to weight-based dosing and/or intra-patient escalation will be considered during the course of the trial, if emerging clinical data suggest that this could be beneficial, for example by reducing any large inter-patient variations in PK.

3.3 Definition of dose limiting toxicity

Therapeutic IgGs such as trastuzumab, alemtuzumab or rituximab, and related proteins commonly cause infusion-related reactions. These reactions are thought to be due to cytokine release and typically are most frequent and severe with the first infusion, declining in incidence and severity thereafter. Such reactions are generally managed by slowing or interrupting the infusion. It is possible that MOv18 IgE will cause these non-specific infusion-related reactions, which are biologically distinct from anaphylaxis, although it can be difficult to distinguish them clinically.

Despite pre-clinical evidence suggesting otherwise, it is possible that MOv18 IgE may also cause anaphylaxis due to basophil and/or mast cell degranulation. Such a reaction would be predicted to persist and probably worsen with subsequent infusions. Slowing or interrupting the infusion would typically be insufficient to control such a reaction and systemic therapy, including administration of adrenaline, might be needed.

Clinically, the symptoms, signs and onset of typical cytokine release-type infusion reactions are very similar to those associated with IgE-mediated basophil and/or mast cell degranulation/anaphylaxis and it may be difficult to distinguish these different types of acute reaction in a patient receiving their first dose. However, the presence of urticaria is almost universal in reactions due to mast cell degranulation, but is not typical of infusion reactions seen with protein-based therapeutics such as IgGs (although it can occur). Importantly, emerging data from the CRUKD14001 study indicate that urticaria without systemic symptoms is common with MOv18 IgE and does not necessarily indicate the onset of anaphylaxis. Serum tryptase elevation (a marker of mast cell degranulation) would not be expected to occur with cytokine release-type infusion reactions (Cheifetz *et al.*, 2003), and for this study is considered critical in distinguishing these two types of reactions clinically.

3.3.1 Dose limiting toxicity (DLT)

Dose limiting toxicity is defined as any of the following events occurring in the first 3 weeks of IMP administration that are considered to be probably or highly probably related to MOv18 IgE:

(For dose-independent significant toxicity, see Section 3.3.2)

Non-haematological toxicity

- Any other drug-related non-haematological Grade 3 or 4 toxicity EXCLUDING:
  - Grade 3 or 4 nausea or vomiting, in patients who have not received optimal treatment with anti-emetics
  - Grade 3 or 4 diarrhoea in patients who have not received optimal treatment with anti-diarrhoeals e.g. loperamide and/or codeine
  - Transient Grade 3 biochemical abnormalities that are asymptomatic and considered not to be clinically significant
  - Grade 3 fatigue
- Fatal event

Haematological toxicity

- Grade 4 neutropenia (ANC < 0.5 x 10^9/L) for ≥ 5 days duration *see note
- Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection with Grade 3 or 4 neutropenia [ANC <1.0 x 10^9/L] and fever ≥ 38.5ºC)
- infection (documented clinically or microbiologically) with Grade 3 or 4 neutropenia (ANC <1.0 x 10^9/L);
- Grade 4 thrombocytopenia (platelets < 25 x 10^9/L)

  a) for ≥ 5 days *see note, or

  b) associated with active bleeding, or

  c) requiring platelet transfusion.

* In the event of a Grade 4 neutropenia or Grade 4 thrombocytopenia, a full blood count must be performed at least five days after the onset of the event to determine if a DLT has occurred. Continue to monitor the patient closely until resolution to Grade 3 or less.

Note that:

- Isolated cutaneous toxicity (urticaria or other skin symptoms/signs) without any associated systemic symptoms or signs and without serum tryptase elevation may not be considered a DLT, if agreed by the Trial Steering Group (TSG) (see Section 3.6 for information regarding the Trial Steering Group). Such patients require premedication (at least for the first subsequent dose) and very close observation if they are given further doses of MOv18 IgE;
- A positive skin prick test is not considered a DLT in this study unless it is associated with systemic symptoms or signs, or an elevated serum tryptase. However, a positive skin prick test is considered an indicator that anaphylaxis might occur if MOv18 IgE were to be given intravenously. Accordingly, positive skin prick tests are an event of interest and must be taken into consideration by the TSG (see Section 3.6) when decisions on dose escalation and/or cohort expansion are made (see also Section 5.5.4).

The dose limiting toxicity (DLT) and maximum tolerated dose (MTD) are defined using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.02.

Should any change be made to the grade or causality of an AE during the study that may alter its DLT status, the Centre for Drug Development (CDD) must be informed immediately as this may affect dose escalation decisions.

3.3.2 Dose-independent significant toxicity

Any event judged to be due to systemic IgE-mediated mast cell degranulation (anaphylaxis; see Appendix 5) is considered to be a dose-independent significant toxicity that may have an impact on the future safe use of IgE therapy. Grade 2 or worse anaphylaxis that is probably or highly probably related to MOv18 IgE is considered clinically important and could lead to temporary suspension of recruitment into the trial and/or other restrictions to patient entry (see Section 3.4.2). Observation of Grade 2 or worse anaphylaxis at a frequency above a pre-determined threshold will lead to permanent cessation of the trial.

3.4 Definition of maximum tolerated dose

3.4.1 Maximum tolerated dose (MTD)

The maximum tolerated dose will be defined as a dose level below the dose level associated with DLT in two out of three patients (or two out of six patients in an expanded cohort). All decisions on dose escalation/de-escalation and cohort expansion/termination will be made by the Trial Steering Group. (see Section 3.6).

It is possible that the MTD will not be reached in this study.

The RP2D will be determined following discussion of all relevant toxicity and efficacy data by the TSG. All significant toxicities (including those occurring after the first three doses of MOv18 IgE) will be considered in the determination of the RP2D.

3.4.2 Acceptable frequency of dose-independent significant toxicity (anaphylaxis)

Anaphylaxis is an unwanted event driven by effector cell degranulation that is usually triggered by exposure to an allergen. Emerging data from the CRUKD14001 trial indicate that anaphylaxis following exposure to Mov18 IgE can occur, but this is unlikely to be dose-related. Patient-specific factors in an affected patient (such as the presence of pre-existing antibodies to IgE) may be involved. Anaphylaxis is reported following exposure to many other medications, although the frequency of such events is generally low. Therefore, the occurrence of anaphylaxis in a single patient in the CRUK14001 trial does not necessarily indicate that a maximum tolerated dose has been reached, or that recruitment overall, cohort expansion, and/or dose escalation should cease in the CRUKD14001 trial.

Accordingly, for anaphylaxis >Grade 1 within this trial (defined according to Appendix 5), an assessment will be made as to the frequency of these events (taking into account events seen in all patients who received MOv18 IgE). An anaphylaxis frequency of 1% or less is likely to be acceptable, but a frequency of 20% or more unacceptable, based on experience with other medications used in routine oncology practice. Therefore, if any patient experiences >Grade 1 anaphylaxis, recruitment will be suspended and a dose review meeting will take place. Taking into consideration the relatively small numbers of patients that are enrolled in a Phase I trial, the TSG will decide whether further patients should be enrolled, whether the dose escalation and/or cohort expansion may continue and whether there should be further restrictions to patient eligibility (if clear risk factors for anaphylaxis can be identified). The TSG will also take into consideration any equivocal or Grade 1 events, should these occur.

3.5 Patient evaluability

All patients who receive any amount of MOv18 IgE, either by IV infusion or as a skin prick test, will be evaluable for safety. However, dose escalation decisions require at least one or three patients (depending on the cohort) to receive 3 doses of IV MOv18 IgE without DLT (see Section 5.4).

All eligible patients who receive at least one dose of IV MOv18 IgE and have a baseline and at least one post-baseline disease assessment will be evaluable for response according to RECIST version 1.1 (see Appendix 3). For this study, to be assigned a status of complete response (CR) or partial response (PR), changes in tumour measurements do not need to be confirmed by repeat measurements four weeks later. To be assigned a status of stable disease (SD), follow-up measurements must have met the SD criteria at least once and at least six weeks after the initial dose of MOv18 IgE is given.

3.6 Trial Steering Group

The TSG is composed of relevant members of the CDD Study Team (including at least one CDD member with the appropriate expertise in the area being discussed), the Chief Investigator (CI), the Chief Scientific Investigator and Principal Investigators (PIs) (a nominated sub- or co-investigator may attend in the PI or CI's place if necessary). The TSG is responsible for reviewing safety and efficacy data on a regular basis and for making decisions on dose escalation, cohort expansion/termination and other aspects of the study. Members should attend dose review meetings (in person or by telephone) and other relevant meetings. Clinical and preclinical immunology/allergy experts are involved, as needed.

Within this protocol there are various examples of when the TSG will be consulted – their involvement is not limited to these situations.

4 PATIENT SELECTION

4.1 Eligibility criteria

The patient must fulfil the eligibility criteria (listed in Sections 4.1.1 and 4.1.2). Please also note excluded concomitant medications (Section 5.7).

4.1.1 Inclusion criteria

1. Histologically or cytologically-proven advanced, unresectable solid tumour of a type known to express FRα in a percentage of cases (see Section 2.4.2).
2. Archival tumour tissue expressing FRα (1+, 2+ or 3+ membrane staining on at least 5% of tumour cells by immunohistochemistry using the BN3.2 antibody, based on the technique described by Lawson & Scorer, 2010).
3. Advanced disease for which no alternative therapy is felt to be appropriate.
4. Measurable disease or disease evaluable by tumour marker. Measurable disease is preferred for patients entering higher cohorts to facilitate efficacy assessments.
5. World Health Organisation (WHO) performance status of 0 or 1 (Appendix 1) and a life expectancy of at least 12 weeks.
6. Haematological and biochemical indices within the ranges shown below. These measurements should be performed within 7 days before the first dose of MOv18 IgE (Day -7 to Pre-dose on Day 1). Measurements performed before Day -7 may be accepted by the CDD to demonstrate eligibility if repeat testing is logistically difficult for the patient and is not considered necessary medically in the opinion of the Investigator or CDD.

Laboratory Test	Value required
Haemoglobin (Hb)	≥ 9.0 g/dL
Absolute neutrophil count	≥ 1.5 x 10^9/L
Platelet count	≥ 100 x 10^9/L
Serum bilirubin	≤ 1.5 x upper limit of normal (ULN)
Alanine aminotransferase (ALT) and aspartate aminotransferase (AST)	≤ 2.5 x ULN unless raised due to liver metastases in which case up to 5 x ULN is permissible
Serum creatinine	≤ 1.5 x ULN

7. Aged 16 years or over at the time consent is given.
8. Written (signed and dated) informed consent and capable of co-operating with treatment and follow-up.

4.1.2 Exclusion criteria

1. Radiotherapy (except for palliative reasons), endocrine therapy, immunotherapy or chemotherapy during the previous four weeks (six weeks for nitrosoureas and mitomycin-C).

   Investigational medicinal products during the previous 4 weeks, or 5 product half-lives before treatment.
2. Patients on beta-blockers and unable to interrupt beta-blockade (which may counteract the therapeutic effects of adrenaline), or tricyclic anti-depressants/MAOIs (which can dangerously augment the effects of adrenaline). These agents should be discontinued at least 4 half-lives before administration of the first dose of MOv18 IgE and for the duration of MOv18 IgE therapy.
3. Patients on bisphosphonates or treated with bisphosphonates in the last 18 months.
4. Ongoing toxic manifestations of previous treatments that have not resolved to Grade 1 or lower (other than alopecia of any grade or Grade 2 peripheral neuropathy).
5. Known brain metastases that have not been previously treated and been stable for at least 2 months.

6. Female patients who are able to become pregnant (or already pregnant or lactating). However, those female patients who have a negative serum or urine pregnancy test before enrolment and agree to either sexual abstinence* or to use two highly effective forms of contraception (oral, injected or implanted hormonal contraception and condom; have an intra-uterine device and condom; diaphragm with spermicidal gel and condom) effective at the first administration of IMP, throughout the study and for six months afterwards are considered eligible.
7. Male patients with partners of child-bearing potential (unless they agree to take measures not to father children by using one form of highly effective contraception at the first administration of IMP, throughout the study and for six months afterwards) or agree to sexual abstinence*. Men with pregnant or lactating partners should be advised to use barrier method contraception (for example, condom plus spermicidal gel) to prevent exposure to the foetus or neonate.
8. Major thoracic or abdominal surgery from which the patient has not yet recovered.
9. At high risk from the effects of anaphylaxis because of non-malignant systemic disease including active uncontrolled infection, cardiac failure, peripheral vascular disease, previous cerebrovascular accident (CVA), dyspnoea due to heart failure, extensive lung metastases, significant pleural effusions or other conditions.
10. History of laryngeal oedema, uncontrolled or high-risk asthma (according to Global Initiative for Asthma (GINA) guidelines – see Appendix 7), or anaphylaxis. Patients with a history of hypersensitivity to carboplatin, taxanes, or contrast media may enter the study at the investigator's discretion.
11. Patients with any congenital or acquired immunodeficiency syndrome or receiving immunosuppressive therapy (including any dose of systemic corticosteroids), or who are immunosuppressed post organ transplant. However, patients receiving inhaled corticosteroids and patients with a history of allergy (other than anaphylaxis) are eligible, as are patients with a history of auto-immune disease.
12. Known to be serologically positive for hepatitis B, hepatitis C or human immunodeficiency virus (HIV).
13. Patients with baseline elevation in serum tryptase (indicating possible mastocytosis) or a positive baseline basophil activation test (indicating a hypothetical potential for anaphylaxis with MOv18 IgE).
14. Participating or planning to participate in another interventional clinical trial, whilst taking part in this study. Participation in an observational study or in the follow-up phase of a previous interventional trial is acceptable.
15. Any other condition which in the Investigator's opinion would not make the patient a good candidate for the clinical study.
16. Patients unwilling or unable to interrupt antihistamines (which may interfere with skin prick testing). Antihistamines should be discontinued at least 4 half-lives before the first skin prick test (see Section 5.7 for further information).

* Abstinence is only considered to be an acceptable method of contraception when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

4.2 Patient enrolment

Before enrolling the patient in the trial, the Investigator or designated representative should determine the eligibility of the patient. Please ensure that CDD are notified of any eligibility concerns at least four working days before treatment is planned. Importantly, for this trial, paired pre-treatment and on-treatment tumour biopsies are required for all patients.

Eligible patients must be enrolled in the EDC system by site staff and then registered at the CDD before they start treatment with MOv18 IgE. If the patient is eligible the patient number will be automatically allocated by the EDC system during the enrolment process. The CDD will send confirmation of the patient registration and the assigned dose level to the Investigator following enrolment of the patient. Study treatment may only be administered after confirmation has been received.

5 TREATMENT

5.1 Selection of the Phase I starting dose

In selecting the starting dose and dose escalation scheme for this trial the needs of patient safety were balanced with the desire for anti-tumour efficacy. The starting dose of MOv18 IgE was based on data from a range of sources.

- **Non-clinical studies of rMOv18 IgE**

- **The affinity of MOv18 IgE for the FRα**

- **The affinity of MOv18 IgE for the FcεRI**

- **Normal levels of circulating IgE in healthy humans**

- **Based on previous human experience**

Based on these data the starting dose for this clinical trial could lie in the range 10 µg to 500 mg/kg. However, the pharmacology of IgE suggests that adverse events are most likely to result from the interaction of IgE with effector cells rather than the free antibody or antibody-antigen complex. Therefore, an appropriate starting dose should consider the interaction of the IgE with FcεRI rather than its antigen interactions. As the administered IgE will have to compete with endogenous IgE for effector cell binding, the relative concentration of the two IgEs in serum is considered critical in determining the

effect of MOv18 IgE doses. Accordingly, the clinical starting dose for this study is based on the normal range of circulating IgE. A starting dose of 70 µg or one tenth of the normal circulating IgE level has been selected. A dose of 70 µg of MOv18 IgE is expected to produce a pulse of binding to effector cells before the unbound MOv18 IgE is cleared (IgE has a plasma half-life of 2 days in human). In contrast, endogenous IgEs will continuously be replenished and quickly out-compete MOv18 IgE for effector cell binding.

The 70 µg starting dose is considered to be scientifically justified based on the known pharmacology of IgE in humans. This starting dose is approximately half that estimated based on the affinity of MOv18 IgE for its target antigen, 50 fold higher than that based on its affinity for FcεRI, and six fold greater than the existing human experience of exogenously administered IgE. However, exceeding these lower estimates for the starting dose of MOv18 IgE is considered justified for MOv18 IgE based on existing knowledge of the biology of IgE.

5.2 Selection of the maximum dose

A maximum evaluated dose of 50 mg is proposed. While this dose is lower than that for most IgGs used therapeutically in oncology (e.g., trastuzumab, rituximab, bevacizumab and pertuzumab), the pharmacology of IgE indicates that these doses are sufficient to overwhelm endogenous IgE and produce pharmacodynamic effects.

5.3 Dosing schedule/treatment schedule

Please refer to Figure 3 later in this section for details of the MOv18 IgE dosing schedule.

It is planned that all patients will receive flat doses of MOv18 IgE, without adjustment for body weight or surface area (based on the expected pharmacokinetics and toxicity of an IgE, there is no reason to adjust dosing for body weight or surface area). However, a switch to weight-based dosing, and/or intra-patient escalation will be considered during the course of the trial, if emerging clinical data suggest that this could be beneficial, for example by reducing any large inter-patient variations in PK.

Initial Treatment Period

Patients in all cohorts will receive a total of six doses of MOv18 IgE at 1-week intervals unless dose-limiting toxicity is encountered or the patient develops progressive disease. During this period, three weekly doses will be considered one cycle of treatment.

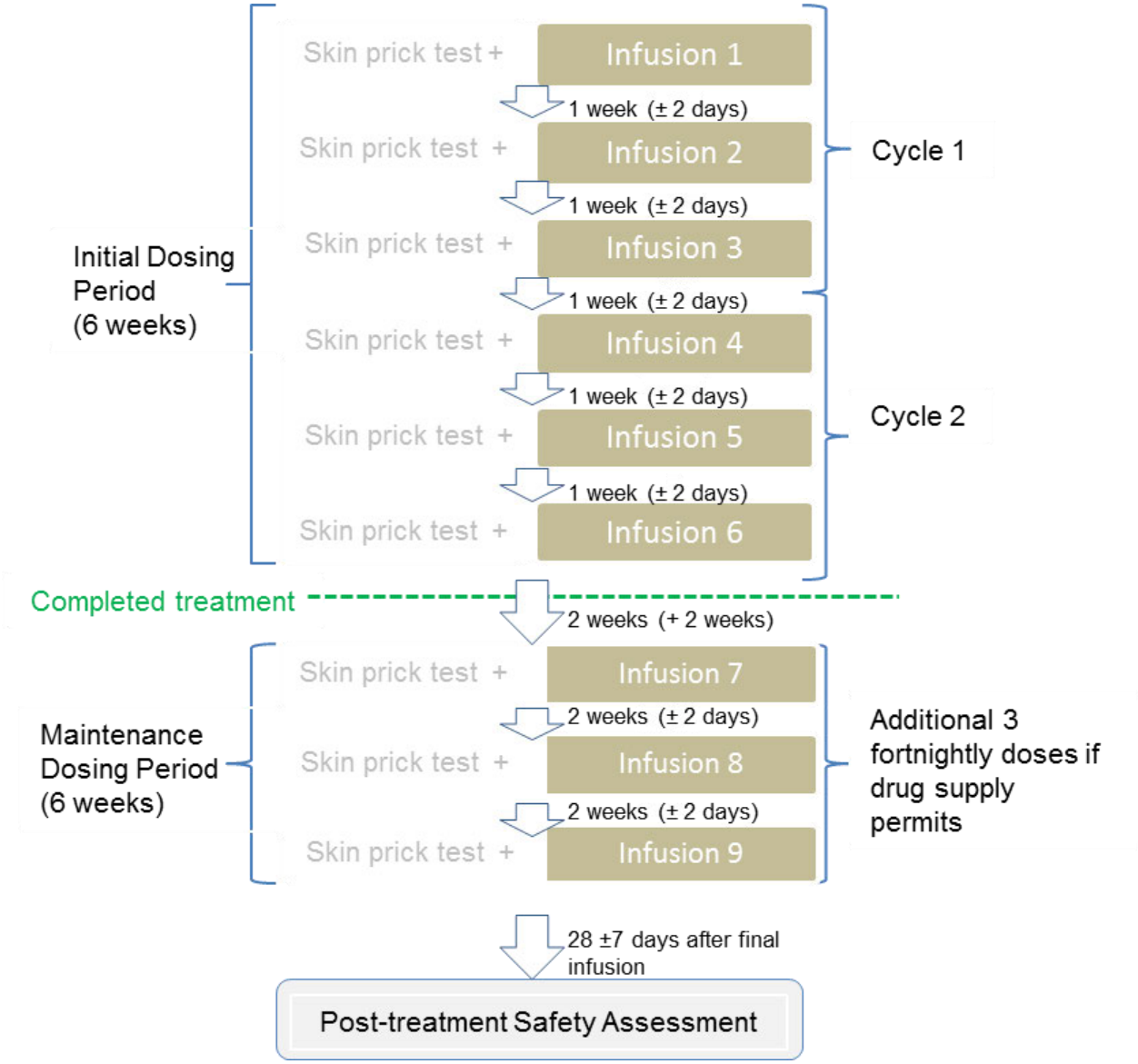
A weekly dosing schedule has been selected for initial dosing of MOv18 IgE due to the relatively short plasma half-life of IgE (2 days) but relatively long tissue half-life (2 weeks). In addition, weekly dosing appeared to be efficacious in the rat model. Weekly administration should result in plasma levels sufficient to maintain occupancy of effector cell FcεRI by MOv18 IgE at higher doses.

Maintenance Period

Should additional drug supply become available during the study (for example, if dose escalation does not proceed through all the planned dose levels), patients in any cohort who appear to be benefitting from MOv18 IgE may be given up to three further doses of MOv18 IgE at fortnightly intervals continuing at the same dose level as the last administered dose (unless dose-limiting toxicity is encountered or the patient develops progressive disease). Ideally, the first maintenance dose of MOv18 IgE will be given two weeks after the sixth dose of MOv18 IgE. However, a gap of up to 4 weeks will be allowed.

A two-weekly dosing schedule has been selected for ‘maintenance’ dosing (which will only take place if drug supply permits). This choice is based on the expected long tissue half-life of MOv18 IgE which suggests that six weekly doses will have effectively ‘loaded’ the patient with MOv18 IgE-bound to effector cells in the tissues.

Figure 3: MOv18 IgE Dosing Schedule



5.3.1 Study drug administration

All patients will receive their first two doses of MOv18 IgE as an IV infusion over 90 minutes (+/-15 mins). A shorter infusion time for subsequent doses of 60 minutes (+/-10 mins) will be allowed if no infusion-related reactions or other allergic reactions are encountered after two doses have been administered. A longer infusion time for subsequent infusions will also be allowed if required in order to manage infusion related cutaneous toxicity. Patients should remain in the clinic for observation for at least one hour after every dose of MOv18 IgE.

The study will be undertaken at investigational centres staffed and equipped to manage medical emergencies and with intensive care facilities. If the patient experiences an event related to study drug that requires intensive clinical care, the Sponsor must be notified immediately.

Patients will be admitted overnight after the first two doses to facilitate intensive safety monitoring procedures. At the investigator's discretion, the requirement for admission may be waived for the second dose if the patient experiences no clinically important adverse events related to MOv18 IgE during the infusion and observation period.

Pre-medication will be administered prior to the first dose in later cohorts if deemed medically appropriate. See Section 5.4

The patient will be intensively monitored during their first two infusions, with measurement of vital signs (blood pressure, pulse rate and temperature) every 15 minutes from the start of the infusion until 30 minutes after completion of the infusion. If no changes are seen, during the first two infusions, then for subsequent infusions vital signs will be assessed 15 minutes and 30 minutes after completion of the infusion. Continuous monitoring with a pulse oximeter is required throughout each infusion until 30 minutes after completion.

If the patient experiences symptoms suggestive of an infusion-related reaction or cytokine release (such as fever, chills, and myalgia), the infusion must be slowed or interrupted and the patient must be treated with oxygen, paracetamol, antihistamines, fluid resuscitation and/or steroids, as clinically indicated. If the reaction does not respond to these conservative measures or is > Grade 2 in severity, the algorithm for the treatment of anaphylaxis must be followed (Appendix 4). Note that for the purposes of this protocol, infusion-related symptoms and signs (such as fever, myalgia, and hypotension) will be recorded and graded individually according to NCI-CTCAE Version 4.02. Grading of systemic mast cell degranulation (anaphylaxis) is defined in Appendix 5 and grading of cytokine release syndrome is defined in Appendix 6, but the distinction between these two events and grading of these events will be performed only in retrospect when results of serum tryptase assays are available, and will thus not be relevant for the management of acute events at the time of infusion. A blood test for measurement of serum tryptase will be taken on completion of all infusions. Additional blood samples for serum tryptase levels should be taken in patients who experience a suspected anaphylactic reaction, such as urticaria and/or severe infusion-related symptoms necessitating interruption or discontinuation of the infusion. Additional samples for serum tryptase should also be taken for patients with a positive skin prick test (see study lab manual and protocol section 7.2 for time points). For details on grading and reporting of infusion-related events and anaphylaxis see Section 7.2.5.

The following medications must be available at the bedside for use in case of an immune-mediated reaction: epinephrine (0.5-1mL IM injection 1:1000), chlorphenamine 10 mg IV/IM injection, paracetamol 1 g orally, hydrocortisone 200 mg IM or IV; oxygen (see 16.4 Appendix 4: Treatment of Anaphylaxis).

For patients who are enrolled in an intra-patient escalation cohort, and receive a higher dose in Cycle 2, the following additional measures will apply:

- In Cycle 1 **and** in Cycle 2 all patients will receive their first two doses of MOv18 IgE as an IV infusion over 90 minutes (+/-15 mins). A shorter infusion time for subsequent doses of 60 minutes (+/-10 mins) will be allowed if no infusion-related reactions or other allergic reactions are encountered after two doses at each dose level have been administered. A longer infusion time for subsequent infusions will also be allowed if required in order to manage infusion related cutaneous toxicity.
- Patients will be admitted overnight after the first two doses in Cycle 1, and the first two doses in Cycle 2 to facilitate intensive safety monitoring procedures. The requirement for admission may be waived for the second dose in each cycle at the investigator's discretion.
- Patients will be intensively monitored during their first two infusions (Cycle 1 doses 1 and 2) and in Cycle 2 (doses 4 and 5 at the increased dose level), the same monitoring will be performed as for Cycle 1.

5.4 Dose escalation scheme

The planned dose escalation scheme is summarised in Table 1. Additional cohorts may be added to evaluate intermediate dose levels or to evaluate alternative dosing schedules, depending on emerging safety information and/or pharmacokinetic data if available. Non-clinical studies have indicated that efficacy in rat xenograft models occurs at 5 to 10 mg/kg. This equates to a surface-area scaled human dose of approximately 50 to 100 mg. However, the plasma half-life of IgE in rat is considerably shorter than in human (12 hours versus 2 days) (Hanashiro *et al.*, 2001, 2002). Efficacious doses in the rat were associated with plasma rMOv18 IgE levels sufficient to represent at least 50% of total plasma IgE

for several days after each dose. This is expected to result in a prolonged wave of rMOv18 IgE loaded effector cells entering tissues.

It was originally estimated that in humans a dose of 10 to 25 mg/patient would be required to produce a similar effect (dependent on the patient's endogenous IgE levels). A flat dose escalation scheme, and a possible intra-patient escalation scheme, is therefore proposed which rapidly ascends (using single-patient cohorts) to doses likely to compete with endogenous circulating IgE and then proceeds with more patients per cohort as endogenous IgE levels are exceeded.

Table 1: Planned dose escalation scheme (Flat Dosing)

Cohort	Dose level	Planned no. patients/cohort	Actual no. patients/cohort
1	70 µg	1	2
2	250 µg	1	8
3	500 µg	1	6
4	700 µg	1	3
5	1.5 mg	3	3
6	3 mg	3	3
7	6 mg	3	TBC
8	12 mg	3	TBC
9	25 mg	3	TBC
10	50 mg	3	TBC

As of October 2020, recruitment to Cohort 6 (3mg) has been completed and the trial protocol has been amended to allow intra-patient dose escalation (see Section 5.4.1)

Initially, patients were enrolled in cohorts of one patient (Cohorts 1-4; 70 – 700 µg doses of MOv18 IgE) as the planned doses were low (based on a conservative approach to safety) and were considered unlikely to provoke a significant biological response. In case of toxicity at these dose levels, an additional two to five patients could be added to better evaluate safety.

For Cohorts 5-10 (flat dosing) (1.5 - 50 mg doses of MOv18 IgE), three patients will be enrolled per cohort, with an additional three patients added to a cohort if needed for toxicity, as outlined below (Table 2). No further dose escalation is planned after Cohort 10 (i.e. 50 mg will be the top dose evaluated). For Cohorts 7-9 (intra-patient escalation), a minimum of 1 patient will be enrolled per cohort (see 5.4.1).

If drug supply permits, one or more cohorts may be expanded up to six patients to further explore the safety and efficacy of MOv18 IgE.

One or more cohorts may be repeated but with administration of prophylactic medication (antihistamine, antipyretic and/or corticosteroid), if considered medically appropriate by the Trial Steering Group (see Section 3.6). Under these circumstances, the prophylactic medication should be given after the skin prick test (before IV administration of MOv18 IgE). Any prophylactic medication will be used within its marketing authorisation.

Before commencement of a new cohort, all patients treated at the previous dose level must have received at least three doses and completed at least three weeks since the first dose. For the second patient in any cohort, the first patient in that cohort must have received at least two doses and been followed for at least 24 hours after the last dose. The second, third and subsequent patients in a cohort (if needed) must not receive their first treatments on the same day. If a patient is withdrawn from the study prior to receiving three doses of study medication without experiencing a DLT or a positive skin prick test, a replacement patient will be added to that dose level.

Decisions on dose escalation will be based primarily on toxicities encountered after the first two doses of MOv18 IgE in each cohort (see Table 2),or the first two doses of cycle 2 for patients undergoing intra-patient dose escalation. However, if available, data on toxicities occurring after later doses will also be taken into consideration. The decision to start a new cohort, and selection of the MOv18 IgE dose for each cohort, will be agreed by investigators and sponsor on review of the toxicities experienced by the preceding cohort during the three-week period from first dosing of each patient. The availability of paired pre-treatment and on-treatment tumour biopsies will also be taken into consideration in decisions on starting a new cohort since paired tumour biopsies are required for all patients.

Based on emerging safety information, prophylactic medication (antihistamine, antipyretic and/or corticosteroid), will be given ahead of the patient's **first and subsequent** infusions if considered medically appropriate by the PI and Sponsor. Under these circumstances, the prophylactic medication should be given after the skin prick test (before IV administration of MOv18 IgE). Any prophylactic medication will be used within its marketing authorisation.

Table 2: Dose escalation decision-making

No. Patients with DLT	Action
0/1 (Cohorts 1-4 only)	Increase to next level
0/3	Increase to next level
1/3	Accrue 3 more pts at same dose level
1/3 + 0/3	Increase to next dose level
1/3 +1/3*	Stop: recommend previous dose level
1/3 + 2/3*	Stop: recommend a lower dose level
1/3 + 3/3*	Stop: recommend a lower dose level
2/3*	Stop: recommend previous dose level
3/3*	Stop: recommend a lower dose level

*No additional patients will be added to a cohort after a second DLT is observed. Should DLT occur in more than 2/3 or 2/6 patients in a cohort, the previous dose level may not be the most appropriate RP2D.

Note: Dose-independent significant toxicity (anaphylaxis) is not counted as a DLT as shown in Table 2 (above) but may limit recruitment to the trial as a whole as outlined in Section 3.4.2.

5.4.1 Intra-patient dose escalations

The established pattern of predictable and tolerable adverse events in Cohorts 1-6 provides reassurance that accelerated dose escalation could proceed subsequently. Intra-patient dose escalation may be initiated from Cohort 7 onwards in order to evaluate alternative doses, depending on emerging safety information and/or pharmacokinetic data if available. An intra-patient dosing schedule has been proposed as per Table 3.

A dose review meeting will be held following completion of Cycle 1 in Cohorts 7 and above, prior to confirming the intra-patient dose escalation for Cycle 2. Should a patient experience any IMP-related AEs of Grade 2* or higher in Cycle 1, then intra-patient dose escalation will not occur, and the patient will continue to be dosed in Cycle 2 based on the flat dose received in Cycle 1 (See Figure 4).

An additional dose review meeting will be held following completion of Cycle 2 prior to confirming the opening of the next cohort. Should a patient experience any IMP-related AEs of Grade 2* or higher in

Cycle 2, then the decision will be made by TSG based on safety data available to either: expand the Cohort by one patient and repeat Cycle 1 and 2 dose levels, **OR** recruit to the next cohort.

Note: Depending on the outcome of the TSG review where patients have experienced a Grade 2 MOv18 related AE, it may be deemed appropriate to move to the next dose level. Assessment for this will be made on a case by case basis. Grade ≥2 rash will generally not preclude intra-patient dose escalation or opening of the next cohort.

If a DLT is experienced in Cycle 1 or Cycle 2, treatment will be withheld until toxicity resolves to baseline or Grade 1. Upon resolution, if appropriate, MOv18 IgE may be recommenced at a lower dose, or the patient may withdraw from study treatment. The cohort will be expanded, and a decision will be made by the TSG whether to expand the cohort by 1 or 2 patients, depending on the nature of the DLT observed (e.g. its nature, grade, expectedness and clinical significance).

Table 3: Planned intra-patient dose escalation scheme

Cohort	Cycle 1 Dose level	Cycle 2 Dose level	No. planned patients/cohort
7(i)	6 mg	*12mg	1**
8(i)	12 mg	*20mg	1
9(i)	20mg	*40mg	1

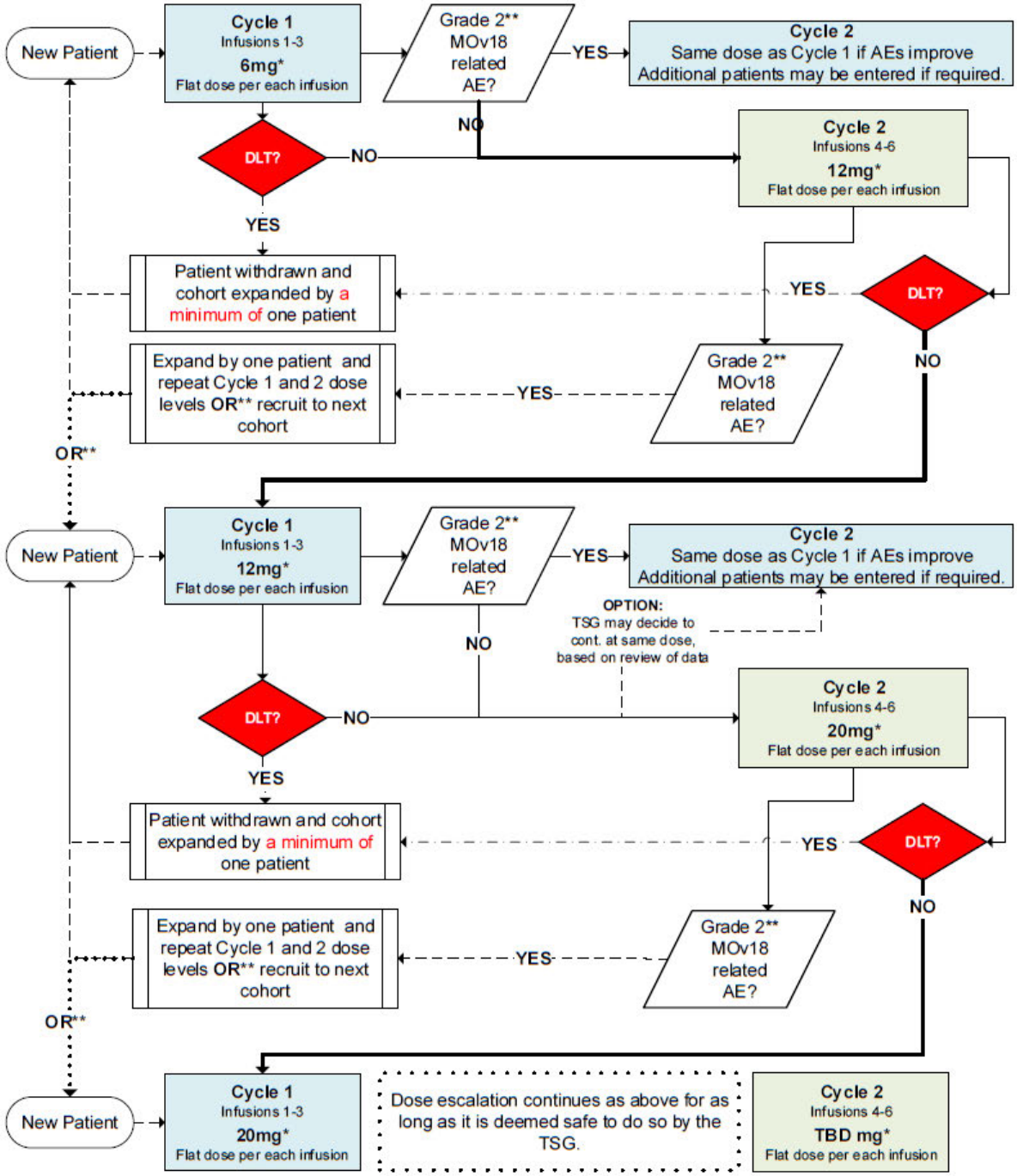
* If required, intermediate dose levels may be explored for the starting dose in Cycle 2, this will be discussed at the dose review meeting and is dependent on the emerging safety profile.

**A minimum of 1 patient will be dosed in each cohort, the final number will be dependent on review of safety data from that dose level.

(i) indicates this is an intra-patient escalation cohort

Figure 4: Intra-patient dose escalation: Example of planned escalation

The TSG to review all data and pay careful consideration to the safety of any current or future patient before making any decisions. Planned escalation may vary from the below based on TSG review of emerging safety data.



*The dose provided is an indicator and may be changed based on emerging data or if intra-patient dose escalation is delayed and the dose level is higher at the point it starts.

**Depending on the outcome of the TSG review where patients have experienced a Grade 2 MOv18 related AE, it may be deemed appropriate to move to the next dose level. Assessment for this will be made on a case by case basis.

5.4.2 Expansion of dose level(s)

If one instance of DLT (as defined in Section 3.3) is observed in up to three patients, then up to six patients will be treated at that dose. If one out of six patients experience a DLT, dose escalation will continue. If two out of up to six (i.e. between two and six) patients experience a DLT, dose escalation will stop, and this dose will be defined as the maximum administered dose (MAD). At least three more patients will be treated at a dose below the MAD to define the MTD.

If any dose-independent significant toxicities (i.e. Grade >1 anaphylaxis, see Sections 3.3.2 and 3.4.2) occur, then the TSG must meet to discuss whether any further patients can be enrolled. See Section 3.4.2.

In case of uncertainty (e.g. patients with a history of immunological reactions to other agents), one or more additional patients with no apparent predisposing factors may be recruited to a dose level to better evaluate toxicity, if agreed by the TSG.

The MAD could also equal the MTD in the event that dose escalation is stopped before two DLTs are observed at a given dose level, due to the expectation that higher dose levels would be too toxic to administer to patients.

5.4.3 Patients enrolled in the intra-patient escalation cohorts

A patient must receive 3 doses of MOv18 IgE without experiencing a DLT in Cycle 1 before they are eligible for intra-patient escalation at a higher dose for Cycle 2. The patient must complete all three doses in Cycle 2 before consideration is given to opening another cohort at a higher dose.

If a patient receives less than 80% of Cycle 1 Dose 1, but tolerates 100% of Doses 2 & 3, the patient will need to receive a full fourth Cycle 1 dose to make them evaluable before consideration of intra-patient dose escalation in Cycle 2. In this situation the treatment course may consist of more than 6 doses.

If a patient has received at least one dose in Cycle 2 but is then withdrawn due to disease progression or other non-clinical reasons prior to completion of treatment, then the TSG will decide whether to expand the current cohort or proceed to the next cohort. This decision will be based on a review of the clinical safety data.

[See Figure 4 “Intra-patient dose escalation” schema for decision making].

5.5 Dose modifications

5.5.1 Dose reductions

Patients experiencing a DLT at any time will have their MOv18 IgE treatment withheld until toxicity resolves to baseline or Grade 1. After resolution, MOv18 IgE may be recommenced at the same dose.

Dose reduction is not generally envisaged but if required (for DLT or other toxicities, other than Grade ≥ 2 anaphylaxis) will be to the next lowest dose according to the dose escalation scheme (Table 1). Only one dose reduction is allowed per patient. Individual patient dose reductions should be discussed and agreed with the CDD.

Patients experiencing Grade ≥ 2 anaphylaxis (see Appendix 5) must discontinue study medication (see Section 3.3.2 and 3.4.2). As per Section 3.4.2, the TSG will also take into consideration any equivocal or Grade 1 events, should these occur. For other infusion reactions (see Appendix 6), continuation of study drug at the same dose level may be appropriate but must be discussed with the TSG.

5.5.2 Dose delays

If at the time of the next planned administration, any drug-related toxicities are still present and have not resolved to Grade ≤ 1 or returned to baseline, the infusion should be delayed for up to two weeks until these toxicities have resolved to Grade ≤ 1 or returned to baseline. If there is no recovery after a two week delay (i.e. the time between doses is three weeks or more), the patient should be withdrawn from the study. Dose delay for reasons other than toxicity should be avoided if possible, but delays resulting from intercurrent illness will not necessarily mandate discontinuation of study treatment.

5.5.3 Dose interruptions

Interrupting or slowing the rate of the infusion may help control infusion-related symptoms (other than anaphylaxis). The infusion may be resumed when symptoms abate. Should repeated infusion interruptions be required, the infusion may be interrupted overnight and resumed the following day. However, this is expected to be a rare occurrence. If a patient receives less than 80% of the planned infusion, then they will be evaluable for safety, but they will not be evaluable for dose review decisions. A patient must have received >80% of 3 infusions before being evaluable for dose review decisions unless otherwise agreed with the TSG.

5.5.4 Dose discontinuations following positive skin prick tests

In general, patients experiencing a positive skin prick test will be withdrawn immediately from study treatment (i.e. they will receive no further IV MOv18 IgE and will undergo no further skin prick testing). However, IgEs have never been administered into the skin before and it is possible that they may be more likely to provoke a positive reaction than other agents. They may also be more likely to provoke cutaneous reactions (without systemic symptoms) when administered IV. The clinical implications of a wheal and flare reaction following skin prick testing of MOv18 IgE is therefore not clear. Accordingly, it is possible that patients may be able to safely receive IV MOv18 IgE (with prophylactic medication and very careful medical supervision) despite a positive skin prick test.

Prior to Protocol Version 5.0, all patients underwent intradermal testing before IV MOv18 IgE administration. Since Protocol Version 5.0, all patients will undergo skin prick testing (instead of intradermal testing) prior to IV MOv18 IgE administration. It is expected that skin prick testing will avoid “false-positive” tests due to non-specific mast cell reactivity (which may be the cause of positive intradermal tests). A decision on whether to allow IV MOv18 IgE administration despite a positive skin prick test will be made by the TSG following a review of patient data from at least 6 patients who have undergone at least two skin prick tests using MOv18 IgE (assuming the first test is negative). A patient experiencing a positive skin prick test on first administration can also be included in this assessment. If 50% or more of 6 patients experience a positive skin prick test (on first or subsequent exposure), without systemic symptoms or signs or serum tryptase elevation, IV dosing in the presence of a positive skin prick test may be explored with the TSG.

The possibility of IV dosing in the presence of a positive skin prick test may be considered by the TSG again at a later date following enrolment of further patients, depending on emerging data (for example, if positive tests without systemic symptoms or signs or tryptase elevation prevent patients receiving further IV MOv18 IgE despite evidence of anti-tumour activity).

5.6 Duration of treatment

A finite number of doses will be administered to each patient. All patients should receive six weekly infusions (two cycles of three weeks) unless (a) the patient asks to be withdrawn, (b) there is evidence of disease progression, or (c) the patient experiences unacceptable toxicity, or (d) for any other of the reasons for withdrawal from the study listed in Section 11. Patients who receive all six infusions in the Initial Dosing Period are considered to have completed study treatment. The duration of treatment will be approximately six weeks followed by a 70-day (+/- 14 days) follow-up period.

As outlined in Section 3.2, drug supply permitting, patients may continue on treatment into the Maintenance Period. These patients may receive an additional three fortnightly infusions of MOv18 IgE.

For these patients, the total treatment duration would be 12 weeks unless treatment stops early because (a) the patient asks to be withdrawn, (b) there is evidence of disease progression, or (c) the patient experiences unacceptable toxicity, or (d) for any other of the reasons for withdrawal from the study listed in Section 11. Treatment will be followed by a 70 day (+/- 14 days) safety follow-up period.

5.6.1 Replacement of patients

If a patient is withdrawn from the study for reasons other than drug-related toxicity or a positive skin prick test and has received less than three infusions of MOv18 IgE during Cycle 1, then this patient can be replaced. The withdrawn patient will be replaced by another patient who will be treated at the same dose level.

5.7 Concomitant medication and treatment

Concomitant medication may be given as medically indicated. Details (including doses, frequency, route and start and stop dates) of the concomitant medication given must be recorded in the patient's medical records and relevant details entered into the electronic case report form (eCRF). Prophylactic medication (antihistamine, antipyretic and/or corticosteroid), will be given ahead of the patient's **first and subsequent** infusions if considered medically appropriate by the PI and Sponsor (See Section 5.4).

Palliative radiotherapy may be given concomitantly for the control of bone pain or other symptoms. Irradiated lesions will not be evaluable for response.

The patient must not receive other anti-cancer therapy or investigational medicinal products during the study.

The following medications are not allowed and must be discontinued before starting study treatment and throughout therapy:

- Beta-blockers (which may counteract the therapeutic effects of adrenaline)
- Tricyclic anti-depressants or monoamine oxidase inhibitors (MAOIs) (which can dangerously augment the effects of adrenaline)
- Systemic immunosuppressive therapy (including any dose of systemic corticosteroids except when prescribed for prevention or treatment of infusion reactions to MOv18 IgE; inhaled corticosteroids are generally allowed)
- Bisphosphonates
- Herbal products, which may have an immunomodulatory effect (e.g. green tea), should generally be avoided but food supplements and homeopathic products are allowed
- Antihistamines (eg. hydroxyzine, cetirizine, loratadine, ketotifen), may interfere with skin prick testing and are not allowed before skin prick testing (see below for washout period). They may be used after a skin prick test when prescribed for prevention or treatment of infusion reactions to MOv18 IgE.
- Omalizumab, topical steroids or topical calcineurin inhibitors in the region used for skin prick testing. These may all interfere with skin prick testing

A washout period of at least four half-lives is required for beta-blockers, tricyclics and MAOIs before starting study medication. An appropriate washout period should be implemented for corticosteroids (e.g. a few days may be sufficient for low doses given for a short period for appetite stimulation). Patients who have been treated with bisphosphonates in the 18 months before starting study medication are excluded from the trial. Antihistamines should be stopped for at least four half-lives before each MOv18 IgE skin prick test. If required for prevention of infusion reactions, antihistamines must be given after the

skin prick test results are known. If needed to ensure adequate washout of an antihistamine, the MOV18 IgE dose may be delayed.

COVID-19 Vaccinations: Due to the lack of interaction studies with the COVID-19 vaccines and Immunotherapy IMPs, an appropriate wash our period of 1 week has been implemented following any COVID-19 vaccine and infusion with MOv18. This will be a 1-week washout following both the 1st and 2nd vaccine doses. Therefore, MOv18 infusions could take place in between the 2 vaccine doses if necessary, but MOv18 dosing would need to be delayed by 1 week after each vaccination. This washout period will be applicable to any COVID-19 vaccine approved for use by the MHRA.

6 PHARMACEUTICAL INFORMATION

6.1 Supply of MOV18 IGE

A complete certificate of analysis and a Qualified Person (QP) certification must be provided with each batch of MOv18 IgE (IMP) and be retained in the Pharmacy File.

For information on MOv18 IgE and re-ordering of supplies, contact the Clinical Research Associate (CRA)/Clinical Study Manager (CSM) responsible for the study who will arrange further supplies.

MOv18 IgE will be supplied by:

[redacted]

The primary and secondary packaging for the IMP will be labelled according to Eudralex Volume 4: Annex 13 'Investigational Medicinal Products' of the European Union guide to Good Manufacturing Practice (GMP). Prior to despatch of IMP to the clinical trial site a label detailing the investigator name and investigator site name will be added to the secondary packaging at the MIA (IMP) licensed manufacturer in accordance with GMP. An example of the labels can be found in the Pharmacy File.

6.2 Pharmaceutical data

6.2.1 Formulation of MOv18 IgE

MOv18 IgE will be supplied in glass vials as a sterile, pyrogen and particle-free clear colourless solution for dilution prior to infusion. [redacted]

6.2.2 Storage conditions

All supplies must be stored in a secure, limited access storage area.

MOv18 IgE must be stored at 2-8°C and protected from light.

6.2.3 Method of reconstitution

6.2.3.1 Solution for intravenous (IV) infusion

Good aseptic practice must be employed when preparing MOv18 IgE solution for infusion.

The MOv18 IgE solution will be drawn from the supplied vial and injected into a bag for IV infusion containing 250 mL of saline. Please refer to the IMP Handling Guidelines for instructions on the preparation of solution for infusion.

6.2.3.2 Solution for skin prick testing

Solution for skin prick testing will be prepared for each patient from the supplied vial. The target concentration for skin prick testing is 2 µg/mL. Please refer to the IMP Handling Guidelines for instructions on the preparation of solution for skin prick testing.

As of Protocol Version 5.0, patients will only undergo skin prick testing prior to IV MOv18 IgE administration (prior to this, patients received a MOv18 IgE intradermal test dose).

6.2.4 Stability and labelling of the diluted MOv18 IgE

The prepared infusion bag must be stored at 2-8°C and used within 24 hours.

Labelling requirements for the diluted MOv18 IgE can be found in the IMP Handling Guidelines.

6.2.5 MOv18 IgE administration

Before administering MOv18 IgE, the exact dosage must always be double-checked by a second suitably qualified person. All checks and double-checks must be documented (signed and dated) and the documentation must be available for the CRA/CSM to verify.

6.2.6 Vein extravasation/accidental spillages

MOv18 IgE is not a vesicant. Extravasation and accidental spillages should be dealt with according to hospital policy.

6.3 MOv18 IgE accountability

Accurate records of all IMP (MOv18 IgE) shipments, vials dispensed, and all IMP returned must be maintained. This inventory record must be available for inspection at any time by CRAs or CSMs of the Centre for Drug Development (CDD). IMP supplies are to be used only in accordance with this protocol and under the supervision of the Investigator.

The Investigator undertakes not to destroy any unused IMP unless authorised to do so by the CDD. Any unused IMP must be destroyed according to hospital procedures (refer to the study IMP Handling Guidelines for exceptions to this) and properly accounted for using the IMP Destruction Form and also on the IMP Accountability Record. During the course of the study the CRA will check the numbers of vials of MOv18 IgE shipped to the centre, the number used and the number destroyed or returned. The pharmacy will give an account of any discrepancy.

The MOv18 IMP Handling Guidelines will describe any appropriate procedures relating to retention of IMP for investigations. If applicable, the retained IMP and vial should be fully accounted for, and any relabelling fully documented. Where the retained IMP is transferred to an analysing lab, this transfer should be documented appropriately.

7 INVESTIGATIONS SCHEDULE

In cases where a patient has investigations at a different hospital, for example weekly blood samples, then it is the Investigator's responsibility to ensure he/she receives and reviews the reported results. These results must be available for source data verification. Laboratory reference ranges, including effective dates, and evidence of laboratory accreditation must be obtained from all laboratories used.

7.1 Pre-treatment evaluations

Details of all evaluations/investigations for enrolled patients, including relevant dates, required by the protocol must be recorded in the medical records so that the eCRF can be checked against the source data.

Please also refer to the tabulated Schedule of Assessments in Section 7.6.

7.1.1 Archival tumour testing for FRα

An archival tumour specimen must be sent to the central analysing laboratory for assessment of FRα expression by immunohistochemistry (IHC) prior to enrolment on the study. Otherwise, there is no time limit for this assessment. A separate 'FRα testing on stored tumour sample informed consent' is required. 1+, 2+ or 3+ membrane staining on at least 5% of tumour cells is required for inclusion of the patient in the study. For patients with no archival specimen available, a pre-treatment tumour biopsy is mandatory. Such patients will need to consent using section B of the 'Alpha Folate Receptor' informed consent' form.

7.1.2 Obtaining written informed consent

Written informed consent must be obtained from the patient using the 'Main study consent' form before any protocol-specific procedures are carried out, other than archival tumour testing for FRα expression which may be performed prior to obtaining written informed consent for the main study (see Section 7.1.1). The patient must be given adequate time to think about their commitment to the study. If more than 28 days has passed since informed consent was obtained before the start of MOv18 IgE dosing then the Investigator should consider whether repeat consent should be obtained from a patient.

Only the Principal Investigator (PI) and those Sub-Investigator(s) delegated responsibility by the PI, and have signed the Delegation Log, are permitted to gain informed consent from patients and sign the consent form. All signatures must be obtained before the occurrence of any medical intervention required by the protocol (ICH GCP 4.8.8 and 8.3.1.2). The patient should sign in the presence of the PI/Sub-Investigator, therefore the date of the signatures of both the patient and the PI/Sub-Investigator should be the same.

The PI or the Sub-Investigator must inform the patient about the background to, and ensure that the patient is aware of, the following points:

- The known toxicity of the IMP and the possibility of experiencing side-effects.
- That IMP is new and that the exact degree of activity is at present unknown, but that treating him/her will contribute to further knowledge.
- The potential dangers of becoming pregnant (or the patient's partner becoming pregnant) and he/she has been given information about appropriate medically approved contraception (refer to Section 9.7).
- That he/she may refuse treatment either before or at any time during the study and that refusal to participate will involve no penalty or loss of benefits to which they are otherwise entitled.

- The options for routine management of their cancer.

- Whom to contact for answers to pertinent questions about the research and their rights, and also who to contact in the event of a research-related injury.

A copy of the consent form and patient information sheet must be given to the patient to keep and the original consent form and patient information sheet, must be filed in the Investigator Study File (ITF) (unless otherwise agreed that the original consent form will be filed in the medical records and the copies kept in the ITF).

7.1.3 Evaluations within 28 days (Day -28 to Pre-dose on Day 1)

The following must be performed/obtained **within the 28 days before** the patient receives the first infusion of MOv18 IgE. Existing results may be used even where these investigations were performed prior to the patient's provision of informed consent for the study if they were performed within the required time window.

- **Demographic details**
- **Medical history** including prior diagnosis, prior treatment, concomitant diseases and baseline signs and symptoms, concomitant treatment
- **Radiological disease assessment** per RECIST 1.1 (see Appendix 3) including a computerised tomography (CT) scan or magnetic resonance imaging (MRI) scan of the chest, abdomen and pelvis, with additional investigations as clinically indicated
- **Tumour marker**, if applicable for tumour type
- **Full physical examination**, including clinical examination and measurement of palpable or visible tumour lesions per RECIST 1.1 (see Appendix 3)
- **WHO performance status**
- **Height and weight**
- **Vital signs** (blood pressure (BP), pulse rate and temperature)
- **Electrocardiogram** (ECG)
- **Urine sample for urinalysis** - glucose, protein and blood
- [redacted]

Note that all adverse events (AEs), including serious adverse events (SAEs), must be monitored and recorded in the eCRF from the time the patient consents to any protocol-specific procedure (see Section 9 for further details).

7.1.4 Evaluations within seven days (Day -7 to Pre-dose on Day 1)

The following must be performed **within seven days before** the patient receives the first dose and results must be confirmed prior to the patient receiving IMP:

- **Blood sample for clinical laboratory tests**:
    - Haematology – haemoglobin (Hb), white blood cells (WBC) with differential count (neutrophils and lymphocytes) and platelets

- **Coagulation screen** (international normalised ratio (INR), and activated partial thromboplastin time (APTT) value or ratio)
- Biochemistry – sodium, potassium, corrected calcium, phosphate, urea, creatinine, total protein, albumin, bilirubin, alkaline phosphatase (alk phos), alanine aminotransferase (ALT) and aspartate aminotransferase (AST), uric acid

- Female patients able to have children must have a negative result on a human chorionic gonadotropin (HCG) **pregnancy test** (serum or urine test is acceptable)

- **Blood sample for serum tryptase** and basophil activation test (BAT)

- **Research blood samples** – as described in Table 6 Summary of PK and PD Assessments.

7.2 Evaluations during the study

Please refer to Table 6 Summary of PK and PD Assessments and Table 7 Volume of blood required for study-specific tests (see Section 8.3) and to the Study Laboratory Manual for the details of the timing and handling instructions for research blood and tumour biopsy samples.

7.2.1 Safety evaluations with EVERY administration of MOv18 IgE

- **Adverse events and concomitant treatments:**

  Before each MOv18 IgE administration, an assessment of any AE experienced or changes in concomitant treatment since the previous visit must be made by the Investigator or Research Nurse. The start and stop dates of an AE together with the Investigator's assessment of the relationship of the event to treatment with MOv18 IgE and details of concomitant treatments must be recorded in the medical records. All AEs must be graded according to NCI-CTCAE Version 4.02.

- **Skin prick testing with MOv18 IgE**

  As of Protocol Version 5.0, skin prick testing has been selected for optimal detection of potential anaphylaxis to MOv18 IgE. Site staff performing the skin prick test doses will first be trained in this technique by an Allergy nurse experienced in skin prick testing for sensitivity to allergens (once staff are trained, with the site Principal Investigator's approval, they may train other colleagues in the technique).

  For this test, one drop of a 2 µg/mL solution of MOv18 IgE will be placed on onto the forearm skin. Please refer to the IMP Handling Guidelines for instructions on the preparation of the solution for administration. Alongside this test dose, a positive histamine control and a negative saline control will be required. Please refer to Skin Prick Testing Method in Appendix 8 for detailed guidance on the method of administration and interpretation of results. Response to the skin prick test should be checked at 15, 30 and 60 minutes post initiation of the skin prick test, prior to the start of every infusion of MOv18 IgE. If the skin prick test is positive at ANY of the three time points, that will constitute a positive result. Absence of a weal and flare reaction will allow the IV dose to be administered with the expectation that the risk of anaphylaxis is very low.

  - In case of a positive reaction, no further MOv18 IgE will be given and the patient will be followed up for safety and then withdrawn from the trial (see Section 11; and Section 5.5.4 for possible exceptions to this rule). In case of a positive skin test, the following additional samples should be taken:

    - Serum tryptase (immediately*, 2 and 6 hours post onset),

    - BAT assay (immediately* post onset),

- PK (immediately*, 2 and 6 hours post onset),
- [redacted]

*or as soon as possible after onset.

Additional exploratory tests may be performed on these existing samples to elucidate the cause of the reaction on the day of the reaction. Further blood draws may be collected at other time points, as deemed appropriate by the TSG, with the patients documented consent in the patient notes. Approximately 45 mL of additional blood may be collected.

In case of uncertainty as to whether a skin prick test is positive or negative, advice will be sought from the Clinical Immunology team.

- **Vital signs** (BP, pulse rate and temperature) should be performed as clinically indicated and
  - Within the 30 minutes pre-dose
  - Every 15 minutes during the infusion for the first two infusions at least (see Section 5.3.1) and for those patients enrolled in the intra-patient dose escalation part of the trial, monitoring will be performed on Cycle 2 (doses 1 and 2) as per Cycle 1.
  - 15 minutes and 30 minutes after completion of the infusion
  - Before discharge from the clinic.
- **Monitoring with a pulse oximeter** continuously throughout the infusion until 30 minutes after completion of the infusion.
- **ECG** after completion of the infusion.
- **Blood sample for serum tryptase** test – taken on completion of the infusion.

Patients should remain in the clinic for observation for at least one hour after every dose of MOv18 IgE (6 hours for a positive skin prick test).

7.2.2 Additional evaluations for the first administration of MOv18 IgE on Cycle 1 Day 1

- **Vital signs** (BP, pulse rate and temperature) should be performed as described in Section 7.2.1 and additionally
  - 1h, 2h, 4h, 8h, 12h (±1 hour), 18h (±2 hour) and 24h (±2 hours) after completion of the infusion
- **Blood sampling for PK** assessment of circulating MOv18 IgE in serum: 3.5 mL blood sample at 6 time points: Pre-dose, and 30 min (±5 min), 2 h (± 30 min), 4 h (± 30 min), 6 h (± 30 min), 24 h (± 2 h). It is possible that the 30 min sample may be substituted for a 48 h (± 2 h) time point in later cohorts – see study lab manual) post-dose. If a time point has been missed, a sample should be taken as soon as possible and the time recorded.

  For patients enrolled in the intra-patient dose escalation, these additional evaluations will also be performed on Cycle 2 Day 1.

7.2.3 Weekly and fortnightly clinic visits

Patients will be reviewed **weekly (±2 days)** prior to each dose of MOv18 IgE (fortnightly ±2 days during maintenance MOv18 IgE, if given) and the following tests and procedures will be performed:

- **Symptom-directed physical examination**

- **Assessment of adverse events and concomitant medication**
- **WHO performance status**
- **Blood sample for clinical laboratory tests**: Haematology and biochemistry must be performed within 24 hours (± 4 h) before each dose of MOv18 IgE and until 4 weeks after the last dose. At a minimum:
    - Haematology – haemoglobin (Hb), white blood cells (WBC) with differential count (neutrophils and lymphocytes) and platelets
    - Biochemistry - sodium, potassium, calcium, phosphate, urea, creatinine, total protein, albumin, bilirubin, alk phos, ALT or AST, uric acid.
- **Research blood samples** – as described in Table 6 Summary of PK and PD Assessments.
- [redacted]
- [redacted]

7.2.4 Prior to the start of a new cycle of MOv18 IgE treatment (within 24 h before start of infusion on Day 1)

- **Urinalysis** –glucose, protein and blood
- **Tumour marker**, if appropriate for tumour type
- **Assessment of disease response:** required every 2 cycles (6-weekly) based on clinical examination, tumour marker, and CT/MRI for patients with measurable disease. Response will be assessed by RECIST 1.1 criteria (see Appendix 3), as well as by CA125 or other tumour marker (Rustin, 2003) if applicable.

For patients receiving maintenance MOv18 IgE, these tests/assessments should be repeated after 6 weeks (i.e. after the third maintenance dose, if given).

7.2.5 Infusion reactions and anaphylaxis

Patients should be assessed carefully for infusion-related reactions. Since it may not be apparent at the time whether a patient is having a reaction due to cytokine release or mast cell degranulation, and since NCI-CTCAE Version 4.02 criteria overlap for cytokine release syndrome, allergic reaction and anaphylaxis, it is proposed that:

- All infusion-related events are reported as individual AEs (e.g. fever, nausea, myalgia or hypotension). Time of onset and worst grade (according to NCI-CTCAE Version 4.02) should be noted for each event.
- Subsequently, infusion-related events associated with an elevation in serum tryptase will be categorised according to the grading criteria outlined in Appendix 5 for IgE-associated mast cell degranulation (anaphylaxis).
- Urticaria is a characteristic feature of anaphylaxis and is to be regarded with suspicion. Patients who experience <u>any</u> of the following events should have additional samples taken as outlined below:

- Urticaria; symptoms/signs suggestive of mast cell degranulation; a suspected anaphylactic reaction; signs and symptoms suggestive of a severe allergic-type reaction; severe infusion-related symptoms necessitating interruption or discontinuation of the infusion.

Additional Samples:

NB: the additional samples outlined below can replace the existing samples in the Schedule of assessments, if the timepoints overlap. Please take all other samples as per schedule in section 7.6.

- Serum tryptase (immediately*, 2 and 6** hours post onset),
- BAT assay (immediately* post onset, in replacement of existing 2 hour timepoint in schedule),
- PK (immediately*, 2 and 6** hours post onset),
- [redacted]

*Or as soon as possible post onset.

**6 hour samples may be omitted *if* impracticable and clinical suspicion of systemic toxicity is low. This is at the discretion of the treating clinician.

- If a patient clearly shows a pattern of simple urticaria with two separate infusions, with no other systemic signs or symptoms and no other features of anaphylaxis (including normal tryptase results and normal BAT assay results) then, following discussion and confirmation with Sponsor, there may be no requirement for additional samples.
- [redacted]
- [redacted]
- Infusion-related events without an elevation in serum tryptase will be categorised as cytokine release syndrome according to NCI-CTCAE Version 4.02 (Appendix 6).

7.3 Evaluations at First Post-treatment Safety Assessment (28 ±7 days after final dose)

Evaluations at the First Post-treatment Safety Assessment must be performed 28 ±7 days after the final infusion of MOv18 IgE. The following investigations should be done:

- **Symptom-directed physical examination**
- **WHO performance status**
- **Weight**
- **Vital signs**, if clinically indicated
- **ECG**

- **Blood sample for clinical laboratory tests** – Haematology and Biochemistry parameters as detailed in Section 7.1.4

- **Urine sample for urinalysis** – glucose, protein and blood

- **Assessment of AEs and concomitant treatments**

- **Assessment of disease response**: if not performed within previous 28 days per RECIST based on clinical examination, tumour marker, and CT/MRI for patients with measurable disease. Response will be assessed by RECIST 1.1 criteria (see Appendix 3),as well as by CA125 or other tumour marker (Rustin, 2003) if applicable.

- **Tumour marker**, if appropriate for tumour type

- **Research blood samples** as described in Table 6 Summary of PK and PD Assessments (see Section 8.3).

Patients who receive MOv18 IgE as a skin prick test only should be followed for safety until resolution or stabilisation of any AEs/SAEs associated with MOv18 IgE.

7.4 Evaluations at Second Post-treatment Safety Assessment (70 ±14 days after final dose)

- **Symptom-directed physical examination**

- **Assessment of AEs**

For patients who are unable to attend in person for this visit due to concurrent illness, progressive disease or other reasons, the safety assessment may be made by telephone and the sample for PK assessment omitted.

7.5 Follow-up of drug-related AEs

Patients who receive any dose of IV MOv18 IgE will be followed for safety reporting until the Second Post-treatment Safety Assessment. If any drug-related AEs and SAEs (i.e. those considered to have a highly probable, probable or possible causal relationship to MOv18 IgE) are present at this assessment, the patient will be followed up at least monthly afterwards until resolution to baseline or stabilisation of these events, unless the patient starts another anti-tumour treatment. If the patient is experiencing no drug-related AEs at the Second Post-treatment Safety Assessment then no follow-up is required.

Patients who receive MOv18 IgE as a skin prick test only should also be followed for safety at least monthly until resolution or stabilisation of any treatment-related AEs/SAEs.

7.6 Schedule of events

Table 4: Schedule for Initial Dosing Period

Observation/Investigation	**Screening/Baseline**		**Initial Dosing Period (first 6 doses) Evaluations for each 3 week cycle (3 doses)**			**First Post-treatment Safety Assessment**	**Second Post-treatment Safety Assessment**
	Day -28 to Day 1 Pre-dose	Day -7 to Day 1 Pre-dose	Day 1 ± 2 days	Day 8 ± 2 days	Day 15 ± 2 days	28 days ± 7 days after final dose	70 days ± 14 days after final dose
FRα IHC test on archival tumour tissue	X[a]						
Demographics	X						
Medical history	X						
Adverse event evaluation	From date of informed consent, continually review					X[p]	X[p]
Concomitant treatments	From date of informed consent, continually review						
Radiological disease assessment	X		Every 6 weeks			X[q]	
Clinical disease assessment (if applicable)	X		Repeat as clinically indicated			X	
Tumour markers e.g. CA125 (if applicable)	X		Every 3 weeks if clinically appropriate for tumour type			X	
Physical examination	Complete		Symptom-directed, as clinically indicated			Symptom-directed	
WHO performance status	X		X	X	X	X	
Vital signs (BP, pulse rate, temperature)	X		X[g]	X[g]	X[g]	If clinically indicated	
Height	X						
Weight	X					X	
Electrocardiogram (ECG)	X		X[s]	X[s]	X[s]	X	
Tumour biopsy [b]	X			Once between C1D8 and C2D15[u]			
Blood sample for clinical laboratory tests[c]		X	X	X	X	X	

Observation/Investigation	Screening/Baseline		Initial Dosing Period (first 6 doses) Evaluations for each 3 week cycle (3 doses)			First Post-treatment Safety Assessment	Second Post-treatment Safety Assessment
	Day -28 to Day 1 Pre-dose	Day -7 to Day 1 Pre-dose	Day 1 ± 2 days	Day 8 ± 2 days	Day 15 ± 2 days	28 days ± 7 days after final dose	70 days ± 14 days after final dose
Urine sample for urinalysis		X	X			X	
Pregnancy test (if applicable)[d]		X					
Blood for serum IgE (SIgE)[e]		X					
MOv18 IgE skin prick test[f]			**X**	**X**	**X**		
MOv18 IgE administration			**X**	**X**	**X**		
1 h observation post-administration			X	X	X		
Overnight stay after MOv18 IgE infusion			Cycle 1[t]	Cycle 1[t]			
Blood for serum tryptase test[h]		X	X	X	X		
Blood sample for PK[i]			Cycle 1[t]	Cycle 1			
[redacted]	[redacted]						
Blood for basophil activation test (BAT) assay[k]		X	Cycle 1[t]		Cycle 1		
[redacted]	[redacted]						

(a) **FR-α staining of archival tumour material** may be performed >28 days prior to treatment on Day 1 and before obtaining consent for the main study.

(b) [redacted]

(c) **Blood sample for clinical laboratory tests:** Haematology, biochemistry and coagulation screens should be performed for the assessment of eligibility during Screening (Day -7 to pre-dose on Day 1). Measurements performed before Day -14 may be accepted by the CDD to demonstrate eligibility if repeat testing is logistically difficult for the patient and is not considered necessary medically in the opinion of the Investigator or CDD.

Haematology and biochemistry should be performed within the 24 h (± 4 h) prior to each dose.

In the event of a Grade 4 neutropenia or Grade 4 thrombocytopenia, a full blood count must be performed at least five days after the onset of the event to determine if a DLT has occurred. Continue to monitor the patient closely until resolution to Grade 3 or less (see Section 3.3 Dose Limiting Toxicity).

(d) **Pregnancy test** for female patients of child bearing potential.

(e) 1 mL blood sample for assessment of **serum IgE** will be taken at baseline only.

(f) **MOv18 IgE skin prick test** on inner forearm with positive histamine control and negative saline control to be performed at the bedside by a specifically trained nurse. Response to the skin prick test should be assessed at 15, 30 and 60 mins post initiation of the skin prick test, prior to the start of every infusion of MOv18 IgE (see Appendix 8 for test method and instructions on interpretation of results).

(g) **Vital signs (BP, pulse rate and temperature**) should be performed for each infusion of MOv18 IgE within the 30 min (±5min) pre-dose, every 15 min (±5min) during the first and second infusions, 15 min (±5min) and 30 min (±5min) after completion of each infusion, and before discharge from the clinic. For the first infusion only, vital signs are additionally required (±10min) at 1h, 2h, 4h, 8h, 12h, 18h and 24h after completion of the infusion, and as clinically indicated. Monitoring with a pulse oximeter is required continuously throughout each infusion until 30 min after completion of the infusion. For intra-patient dose escalation cohorts, these assessments are to also be performed on Cycle 2 Day 1.

(h) 1 mL blood sample for 200 µL serum for measurement of **serum tryptase** at baseline and on completion of every infusion of MOv18 IgE. Additional samples may be taken in response to a positive skin prick test or in patients who experience a suspected anaphylactic reaction, such as urticaria or severe or infusion-related symptoms necessitating interruption or discontinuation of the infusion (see protocol section 7.2.1 and 7.2.5 for details of when to take these samples). Samples will be analysed and reported prior to next dose for 2nd and 3rd doses. Subsequent samples can be analysed on request of the Investigator in response to clinical symptoms and reported prior to next dose.

(i) 3.5 mL blood sample for 1-2 mL serum for **PK assessment of circulating MOv18 IgE** at 7 time points: Pre-dose on Cycle 1 Day 1 (within 24 h of infusion), 30 min (±5 min)*, 2 h (± 30 min), 4 h (± 30 min), 6 h (± 30 min), 24 h (± 2 h), and possibly* at 48 h (± 2 h) post-dose; Cycle 1 Day 8 Pre-dose; (total blood volume ~25mL). If a time point has been missed, a sample should be taken as soon as possible and the time recorded. *The 30 min (±5 min) sample may be replaced by the 48h (± 2 h) post-dose sample at higher dose cohort levels (refer to the study laboratory manual for which sample to take). Additional samples should be taken at 0, 2 and 6 hours following a suspected anaphylactic/urticarial reaction or positive skin prick test (see protocol section 7.2.1 and 7.2.5 for details).

(j) [redacted]

(k) 6 mL blood sample for **basophil activation test (BAT)** at Day -7 to Pre dose Cycle 1 Day 1 and 2 h (± 30 min) after the end of infusion of MOv18 IgE at the first and third infusions (Cycle 1 Day 1 and Cycle 1 Day 15) (total blood volume 18 mL). Additional samples should be taken immediately (0 hours) following a suspected anaphylactic reaction, urticarial, or severe infusion-related symptoms necessitating interruption or discontinuation of the infusion or positive skin prick test (see protocol section 7.2.1 and 7.2.5 for details). For intra-patient dose escalation cohorts, a sample will also be taken on Cycle 2 Day 1, 2 h (± 30 min) after the end of infusion of the higher dose of MOv18 IgE.

(l) [redacted]

(m) [redacted]

(n) [redacted]

(o) [redacted]

(p) Monthly **follow-up** required ONLY for those AEs and SAEs considered drug-related (highly probable, probable or possible) and present at the Second Post-treatment Safety Assessment. Monthly follow-up to continue until resolution, return to baseline, stabilisation or patient starts another anti-cancer treatment.

(q) All patients, who are removed from the study for reasons other than progressive disease, must be re-evaluated at the time of treatment discontinuation, unless a **tumour assessment** was performed within the previous four weeks.

(r) For patients unable to attend in person for the **Second Post-treatment Safety Assessment** due to concurrent illness, progressive disease or other reasons, the safety assessment may be made by telephone and the sample for PK assessment omitted.

(s) ECG to be performed after completion of the infusion.

(t) For intra-patient dose escalation cohorts, these assessments are to also be performed on Cycle 2 Day 1.

(u) For intra-patient dose escalation cohorts, the post dose biopsy should be performed following at least the first dose in Cycle 2 where possible.

Table 5: Schedule for Maintenance Dosing Period

Observation/Investigation	Screening/ Baseline	Initial Dosing Period	Maintenance Dosing Period (MOv18 IgE dosing every 14 ± 2 days)			First Post-treatment Safety Assessment	First Post-treatment Safety Assessment
			7th dose	8th dose	9th dose	28 days ± 7 days after final dose	70 days +/- 14 days after final dose
Adverse event evaluation	Continually review					As in Table 4	
Concomitant treatments	Continually review						
Radiological disease assessment	As in Table 4	As in Table 4	Every 6 weeks				
Clinical disease assessment (if applicable)			Repeat as clinically indicated				
Tumour markers e.g. CA125 (if applicable)			Repeat as clinically indicated				
Physical examination			Symptom-directed, as clinically indicated				
WHO performance status			X	X	X		
Vital signs (BP, pulse rate, temperature)[a]			X	X	X		
ECG			X				
Bloods for haematology & biochemistry[b]			X	X	X		
Urine sample for urinalysis			X				
MOv18 IgE skin prick test[c]			**X**	**X**	**X**		
MOv18 IgE administration			**X**	**X**	**X**		
1 h observation post-administration			X	X	X		
Blood for serum tryptase test[d]			X	X	X		

(a) **Vital signs (BP, pulse rate and temperature)** should be performed within the 30 min (±5min) pre-dose, 15 min (±5min) and 30 min (±5min) after completion of the infusion and before discharge from the clinic at every infusion of MOv18 IgE and as clinically indicated. Monitoring with a pulse oximeter is required continuously throughout the infusion until 30 min after completion of the infusion.

(b) **Blood sample for Clinical laboratory tests:** Haematology and biochemistry should be performed within 24 h (± 4 h) before dosing for every infusion of MOv18 IgE. In the event of a Grade 4 neutropenia or Grade 4 thrombocytopenia, a full blood count must be performed at least five days after the onset of the event. Patients should be monitored closely until resolution to Grade 3 or less (see Section 3.3 Dose Limiting Toxicity).

(c) **MOv18 IgE skin prick test** on inner forearm with positive histamine control and negative saline control to be performed at the bedside by a specifically trained nurse. Response to the skin prick test should be assessed at 15, 30 and 60 mins post initiation of the skin prick test, prior to the start of EVERY infusion of MOv18 IgE (see Appendix 8 for test method and instructions on interpretation of results). Additional blood samples should be taken in case of a positive test (see Section 7.2.1 and footnotes to Table 4).

(d) 5 mL blood sample for 200 µL serum for measurement of serum **tryptase** at baseline and on completion of every infusion of MOv18 IgE. Additional samples may be taken in response to a positive skin prick test or in patients who experience a suspected anaphylactic reaction, urticarial, or severe infusion-related symptoms necessitating interruption or discontinuation of the infusion (see protocol section 7.2.1 and 7.2.5 for details of when to take these samples). Samples can be analysed on request of the Investigator in response to clinical symptoms and reported prior to next dose.

8 PHARMACOKINETIC AND PHARMACODYNAMIC ASSESSMENTS

Please refer to the Study Laboratory Manual for the names of the analysing laboratories and for detailed instructions for sampling.

Sample collection schemes and frequency of analysis may be reconsidered during the study in response to the reported PK, PD or safety data.

Patients will be asked to consent to the use of leftover blood, ascitic or pleural fluid and tumour tissue for future research into the treatment of cancer using IgE and similar immunotherapies.

8.1 Summary of assessments

See Table 6 Summary of PK and PD assessments and Table 7 Volume of Blood required.

8.2 Secondary assessment - Pharmacokinetics of MOV18 IgE

The $t_{½}$ of IgE in the circulation is known to be approximately two days in man but much longer in the tissues (Gould *et al.*, 2003). The PK sampling time points have therefore been chosen to confirm the hypothesis that MOv18 IgE is cleared from the blood over a timescale that is expected for this antibody class, and to obtain preliminary data to guide further dosing schedules.

3.5 mL of blood will be collected at the following time points on and following Cycle 1 Day 1:

- Within the 24 h pre-dose
- 30 min ±5 min after completion of the infusion (Refer to lab manual whether this or the 48h sample should be taken)
- 2 h ±30 min after completion of the infusion
- 4 h ±30 min after completion of the infusion
- 6 h ±30 min after completion of the infusion
- 24 h ±2 h after completion of the infusion
- 48 h ±2 h after completion of the infusion (Refer to lab manual whether this or the 30min sample should be taken)
- 7 days ±1 day after commencement of the infusion (i.e. Pre-dose Cycle 1 Day 8)

The approximate volume of blood withdrawn from each patient for pharmacokinetic analysis will be 24.5mL. This volume may increase if additional samples are needed as per section 7.2.5.

Additional PK timepoints may be implemented if emerging data suggested that this would be beneficial following discussion between the TSG. The additional timepoints will be on C1D15 and the total blood volume taken will not exceed 17.5 mL.

Serum samples will be prepared at each centre and then frozen on site. They will be shipped to the analysing laboratory on dry ice. MOv18 IgE serum levels will be assayed using an anti-idiotypic enzyme-linked immunosorbent assay (ELISA).

The plasma concentration/time data will be analysed using non-compartmental methods. The PK parameters to be determined for MOv18 IgE include the maximum observed plasma concentration (C_{max}), time to reach C_{max} (T_{max}), the area under the plasma concentration time curve (AUC), and the terminal elimination half-life ($T_{1/2}$).

8.3 Tertiary/research assessments - pharmacodynamics

[redacted]

Table 6: Summary of PK and PD Assessments

Biomarker	Method	Sample/ Quantity per Time point	Rationale	Time points[3]	Timing of analysis
Tumour FRα expression	IHC	Archival tumour tissue	To demonstrate target expression in tumour; required for patient eligibility	Screening	3-5 day turnaround from receipt of sample at laboratory
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serum tryptase	ELISA	1mL blood for 200 µl serum to allow for re-test.	To distinguish between non-specific infusion reaction and anaphylaxis. Validated routine NHS test with normal value 2-14 µg/L.	Day -7 to Pre dose Cycle 1 Day 1; on completion of infusion at each dose. Additional samples in response to clinical symptoms (0, 2 and 6 hours after onset of the reaction). (see Table 4 footnotes).	Analysed and reported prior to next dose for 1st and 2nd doses. Subsequent samples may be reported prior to the next dose on request. Otherwise, batched and analysed at the end of each cohort.
Circulating MOv18 IgE (PK)	ELISA	3.5mL blood for 1-2mL serum	Exposure in plasma and to look at adaptive immunity – FR specific IgE	Cycle 1 Day 1 Pre dose (within 24 h of infusion) and 2h, 4h, 6h, 24h, and either 30min or 48h Post dose (see lab manual); Pre dose Cycle 1 Day 8[5] For Intra-patient escalation cohorts only, as above plus: Cycle 2 Day 1 Pre-dose (within 24 h of infusion) and 2h, 4h, 6h, 24h, and either 30min or 48h Post dose (see lab manual)	Flexible timing; in response to toxicity, to inform dose review decisions or in batches.

Biomarker	Method	Sample/ Quantity per Time point	Rationale	Time points[3]	Timing of analysis
[redacted]					
Basophil activation test (BAT test)	In vitro followed by FACS	6mL whole blood	Measures functional IgE capable of binding to and stimulating basophils	Day -7 to Pre dose Cycle 1 Day 1; 2 h after end of infusion at 1st and 3rd doses [5] For Intra-patient escalation cohorts only, as above plus: Cycle 2 Day 1; 2 h after end of infusion	Within a day of sample being taken (See current lab manual).
[redacted]					
[redacted]					
[redacted]					

Biomarker	Method	Sample/ Quantity per Time point	Rationale	Time points[3]	Timing of analysis
[redacted]					
[redacted]					
[redacted]					

[1] [redacted]

[2] [redacted]

[3] Unless specifically stated otherwise, blood sample timings have a window of +/- 30 minutes for samples taken within 24 hours of an infusion, +/- 2 hours for samples taken at 24 or 48 hours, +/- 1 day for samples up to 28 days after the last dose and then +/- 7 days thereafter (see Section 8.2 for example).

[4] Some assays may be done (in batches) before the end of study.

[5] Additional samples may be taken following a positive skin prick test (see Section 7.2.1) or a suspected anaphylactic reaction (see Section 7.2.5).

[6] [redacted]

Table 7: Approximate volume of blood required for study-specific tests (mL)

Time point		Clinical laboratory tests	3 - BAT	[redacted]	5 - PK	6 - Serum tryptase	7 - Serum IgE	[redacted]	Approximate total to be taken per time point*
Baseline (Day -7 to Pre dose Cycle 1 Day 1)		15	6			1	1		89
Dose 1 (Cycle 1 Day 1)	Pre dose (-24 h)	10			3.5				13.5
	End of infusion					1			5
	30 m				3.5 (or taken at 48hrs)				8.5
	2 h		6		3.5				14.5
	4 h				3.5				8.5
	6 h				3.5				8.5
	24 h				3.5				8.5
Dose 2 (Cycle 1 Day 8)	Pre-Dose (-24 h)	10			3.5				64.5
	Post Dose					1			
Dose 3 (Cycle 1 Day 15)	Pre-Dose (-24 h)	10							69
	Post Dose		6			1			
Dose 4 (Cycle 2 Day 1)***	Pre-Dose (-24 h)	10							20
	Post Dose					1			
Dose 5 (Cycle 2 Day 8)		10				1			15
Dose 6 (Cycle 2 Day 15)	Pre-Dose (-24 h)	10							63
	Post Dose					1			
28 ±7 days after final dose		10							20
Total for assay		85	18		24.5	8	1		
Approximate total to be taken in Initial Dosing Period									407.5

* Total blood volume to be taken per time point has been rounded up to reflect the minimum amount of blood which can be drawn from the patient using the required vacutainers. Additional samples may be taken following a positive skin prick test (see Section 7.2.1) or a suspected anaphylactic reaction (see Section 7.2.5) but patients with a positive skin prick test or a reaction due to mast cell degranulation will generally receive no further MOv18 IgE so the final total volume of blood required for the study is unlikely to exceed the volumes outlined in the table.

** [redacted]

*** If patient is enrolled in an intra-patient escalation cohort then additional blood samples will be taken as per C1D1.

Patients who complete the **Maintenance Period** will have additional fortnightly clinical laboratory tests (10 mL per time point) and a serum tryptase assay after each of the three doses (5mL blood for 200µL serum, per assay), increasing the approximate total volume of blood drawn for study-specific tests to 365.5 mL.

9 ASSESSMENT OF SAFETY

Potential risks of MOv18 IgE therapy based on mechanistic and preclinical data for MOv18 IgE, and clinical data for other therapies directed against the FRα include:

- Anaphylaxis
- Infusion reactions/cytokine release
- Risks related to FRα targeting
- Anti-drug antibody (ADA) formation

Monitoring and management of infusion reactions and anaphylaxis are described in Sections 7.2.1 and 7.2.5, and Appendix 4.

Side effects due to FRα–targeting in normal tissues are not anticipated with MOv18 IgE since FRα expression is generally low in normal tissues and likely to be inaccessible to MOv18 IgE in many organs (for example, expression in renal tubules is endoluminal). Moreover, no unequivocal reports of such side effects have been found in the literature for other FRa-targeted agents. However, should it occur, FRα–targeting in normal tissues could result in renal, pulmonary, intestinal or CNS toxicity (manifest for example, as glomerulonephritis, interstitial pneumonitis, gastro-enteritis or neuro-inflammatory symptoms). Such side effects should be detected by routine clinical monitoring for AEs and laboratory abnormalities within the trial. If identified, treatment should be symptomatic/supportive along with cessation of MOv18 IgE therapy, if clinically indicated. Immunosuppressive medication (for example corticosteroids) could potentially be required for severe normal tissue toxicity Supportive treatment could include analgesics and/or anti-inflammatory medication, oxygen, antibiotics, fluid replacement therapy, anti-diarrhoeals, histamine (H2) antagonists etc, depending on the organ(s) affected.

In theory, inflammation, pain or tenderness at sites of bulky disease could also occur. Treatment should be with conventional analgesia, as needed.

Anti-drug antibody (ADA) formation is not expected with MOv18 IgE since it was not reported in clinical studies of MOv18 IgG. Nevertheless, it could occur since ADA formation has been reported with other chimeric IgGs, such as rituximab. ADA formation following MOv18 IgE exposure could potentially result in worsening of infusion reactions with subsequent MOv18 IgE infusions, loss of efficacy of MOv18 IgE resulting in clinical deterioration, or hypersensitivity reactions when treated with other diagnostic or therapeutic monoclonal antibodies. [redacted]

Tumour lysis syndrome is not expected to occur with MOv18 IgE but all patients will be monitored with regular serum uric acid levels (additional assessments of uric acid levels will be made if clinically indicated). Treatment with hydration, allopurinol and/or rasburicase should be initiated if clinically indicated.

9.1 Investigator Responsibilities

The investigator is responsible for monitoring the safety of patients who have enrolled in the study and for accurately documenting and reporting information as described in the following sections.

9.1.1 Medical Cover

The Chief/Principal Investigator is also responsible for ensuring patients have access to 24 hour advice and/or care. Patients will be provided with the necessary contact numbers for both normal working and out of hours care. A copy of the protocol must be made available out of hours to ward staff and clinicians

on call so that the appropriate advice may be given to the patient, the patient's relative or other care giver (for example GP). The Chief/Principal Investigator must ensure that should the on call clinician or ward staff require more advice than is in this protocol, that they have access to the Investigator or delegated members of the investigator's team who can answer any questions.

9.2 Adverse event definitions

9.2.1 Adverse event

An adverse event (AE) is any untoward, undesired or unplanned occurrence in a patient administered an IMP, a comparator product or an approved drug. An AE can be a sign, symptom, disease, and/or laboratory or physiological observation that may or may not be related to the IMP or comparator.

An AE includes but is not limited to those in the following list.

- A clinically significant worsening of a pre-existing condition. This includes conditions that may resolve completely and then become abnormal again.
- AEs occurring from an overdose of an IMP, whether accidental or intentional.
- AEs occurring from lack of efficacy of an IMP, for example, if the Investigator suspects that a drug batch is not efficacious or if the Investigator suspects that the IMP has contributed to disease progression.

9.2.2 Serious adverse events

A serious adverse event (SAE) is any AE, regardless of dose, causality or expectedness, that:

- results in death;
- is life-threatening*;
- requires in-patient hospitalisation or prolongs existing in-patient hospitalisation (some hospitalisations are exempt from SAE reporting – e.g. hospital admissions planned prior to the patient entering the trial; overnight stays for planned procedures such a blood transfusion (see Section 9.4.1);
- results in persistent or significant incapacity or disability;
- is a congenital anomaly or birth defect;
- is any other medically important event**.

* A life-threatening event is defined as an event when the patient was at substantial risk of dying at the time of the adverse event, or use or continued use of the device or other medical product might have resulted in the death of the patient.

**A medically important event is defined as any event that may jeopardise the patient or may require intervention to prevent one of the outcomes listed above. Examples include allergic bronchospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalisation. The development of drug dependence or drug abuse would also be examples of important medical events.

For fatal SAEs, wherever possible report the cause of death as an SAE with a fatal outcome rather than reporting death as the SAE term. When available the autopsy report will be provided to the Sponsor.

If during the course of the study, other medically important events are identified and there is a requirement to report specific events outside of the standard criteria, this will be communicated to site and the protocol will be updated to reflect this.

Trial–specific medically important events: Anaphylaxis is considered to be a dose-independent significant toxicity that may have an impact on the further conduct of this trial. Therefore, all events of anaphylaxis, regardless of severity, must be reported as SAEs.

Any dose limiting toxicity (DLT) must be reported to the CDD Clinical Study Manager (CSM) and CRA within 24 hours of site staff becoming aware of the DLT. The CDD Pharmacovigilance Department must be copied into any initial email notification. (See Section 3.3.1)

Other reportable events that must be treated as SAEs are listed below.

- Pregnancy exposure to the IMP. Any pregnancy occurring in a patient or a patient's partner during treatment with an IMP or occurring within six months of the last IMP administration, must be reported to the Pharmacovigilance Department in the same timelines as an SAE. These should be reported even if the patient is withdrawn from the trial.
- Overdose with or without an AE (any dose above that specified in the protocol, not necessarily intentional).
- Inadvertent or accidental exposure to an IMP with or without an AE, including for example, spillage of the IMP that contaminates staff.
- Any AE that could be related to the protocol procedures, and which could modify the conduct of the trial.
- **A positive skin prick test** is considered an event of interest in this trial since it indicates that anaphylaxis might occur if MOv18 IgE were to be administered IV. Therefore, all positive skin prick tests must be reported to PV as an SAE within 24 hours.

9.2.3 Suspected, unexpected, serious, adverse reactions

A SUSAR is a suspected, unexpected, serious adverse reaction.

All AEs and SAEs will be assessed by CDD for seriousness, causality and expectedness. The Pharmacovigilance Department will expedite all SUSARs to the relevant competent authority/authorities and the relevant Ethics Committee(s) within the timelines specified in legislation (SI 2004/1031 as amended).

9.2.4 Causality

The relationship of an AE to the IMP is determined as follows.

Highly probable • Starts within a time related to the IMP administration and • No obvious alternative medical explanation.
Probable • Starts within a time related to the IMP administration and • Cannot be reasonably explained by known characteristics of the patient's clinical state.
Possible • Starts within a time related to the IMP administration and • A causal relationship between the IMP and the AE is at least a reasonable possibility.
Unlikely • The time association or the patient's clinical state is such that the trial drug is not likely to have had an association with the observed effect.
Not related • The AE is definitely not associated with the IMP administered.

Note: Drug-related refers to events assessed as possible, probable or highly probable.

The Investigator must endeavour to obtain sufficient information to determine the causality of the AE (i.e. IMP, other illness, progressive malignancy etc) and must provide his/her opinion of the causal relationship between each AE and IMP. This may require instituting supplementary investigations of significant AEs based on their clinical judgement of the likely causative factors and/or include seeking a further opinion from a specialist in the field of the AE.

The following guidance should be taken in to account when assessing causality of an AE:

- Previous experience with the IMP and whether the AE is known to have occurred with the IMP.
- Alternative explanations for the AE such as concomitant medications, concurrent illness, non-medicinal therapies, diagnostic tests, procedures or other confounding effects.
- Timing of the events between administration of the IMP and the AE.
- IMP blood levels and evidence, if any, of overdose.
- De-challenge, that is, if the IMP was discontinued or the dosage reduced, what happened to the adverse reaction?
- Re-challenge, that is, what happened if the IMP was restarted after the AE had resolved?

9.2.5 Expectedness

Assessment of expectedness will be made by the Pharmacovigilance Department against the current version of the MOv18 IgE Investigator's Brochure.

9.3 Collection of safety information

9.3.1 Screening failures

For screening failures, SAEs must be reported to the Pharmacovigilance Department, CDD from the date of consent until the date the patient is confirmed as ineligible.

9.3.2 Eligible patients

For eligible patients, SAE and AE collection and monitoring will commence at the time the patient gives their written consent to participate in the trial and will continue until the Second Post-treatment Safety Assessment 70 ±14 days after the last administration of MOv18 IgE or until the patient starts another anti-cancer therapy.

Should an Investigator become aware of any drug-related SAEs after the patient's final study visit, these must also be reported to the CDD within the expedited timelines stated above.

9.3.3 Follow-up of AEs and SAEs

Follow-up of AEs with a causality of possible, probable or highly probable will continue until the events resolve, stabilise or the patient starts another anti-cancer therapy.

The Pharmacovigilance Department will make requests for further information on SAEs to the trial site at regular intervals. Requested follow-up information should be reported to the Pharmacovigilance Department in a timely manner and as soon as possible after receipt of the follow-up request. For fatal or life-threatening cases, follow-up information should be reported to the Pharmacovigilance Department as soon as possible.

9.3.4 Other safety information of interest

We are also interested in collecting information on the following situations, whether they are associated with an AE or not:

- Abuse or misuse
- Occupational exposure (to a person other than the patient, for example spilling of IMP on hands of nurse or splashing in the eye).

Any occurrences of these should be reported in the same manner as SAEs (Section 9.4).

9.4 Reporting of SAEs to the Pharmacovigilance Department, CDD

All SAEs, regardless of causality, must be reported to the Pharmacovigilance Department in an expedited manner. SAEs should be documented on an SAE report form, using the completion guidelines provided.

The SAE report form should be emailed to Pharmacovigilance Department within 24 hours of site staff becoming aware of the SAE.

[redacted]

Each episode of an SAE must be recorded on a separate SAE report form. The NCI-CTCAE Version 4.02 must be used to grade each SAE, and the worst grade recorded. If new or amended information on a previously reported SAE becomes available, the Investigator should report this to the Pharmacovigilance Department on a new SAE report form.

If the SAE has not been reported within the specified timeframes, a reason for lateness must be added on the form when sending the SAE report to the Pharmacovigilance Department.

Should the investigator become aware of any drug-related SAEs after the patient has withdrawn from the study, these must also be reported to the PV Department within the timelines specified above.

9.4.1 Events exempt from being reported as SAEs to the Pharmacovigilance Department

Events specified in this section do not require reporting as SAEs in this trial, unless hospitalisation is prolonged for any reason and then an SAE form must be completed. The events must still be recorded in the appropriate section of the electronic case report form (eCRF).

Elective admissions to hospital for procedures which were planned prior to entering the trial are not SAEs. Hospitalisation for administration of the IMP according to the trial protocol is also exempt from being reported as an SAE, unless the patient experiences an event during the admission which would normally qualify as an SAE.

Death due to disease progression does not require expedited reporting unless considered related to the IMP.

9.5 Recording of adverse events and serious adverse events in eCRFs

All AEs, including SAEs, must be recorded in the eCRF for eligible patients. All concomitant medications, including herbal medications and supplements must be recorded. Any therapy used to treat the event must be recorded. The eCRF will be reconciled with the safety database regularly during the trial and at the end of the trial. Therefore, the sites should ensure the data entered on the SAE report form and the data entered into the eCRF are consistent. The CDD Medical Advisor and the Investigator(s) will regularly review the safety data from both the safety and the clinical database.

9.6 Urgent safety measures

The Sponsor or Investigator may take appropriate urgent safety measures (USMs) in order to protect the patient of a clinical trial against any immediate hazard to their health or safety. This includes procedures taken to protect patients from pandemics or infections that pose serious risk to human health.

USMs may be taken without prior authorisation from the competent authority.

The Medicines and Healthcare products Regulatory Agency (MHRA) and the Main Research Ethics Committee (REC) must be notified within three days of such measures being taken.

Should the site initiate a USM, the Investigator must inform the Sponsor immediately either by:

- [redacted]
- [redacted]

The notification must include:

- the date of the USM;
- who took the decision; and
- why action was taken.

The Sponsor will then notify the MHRA and the Main REC within three days of USM initiation.

9.7 Pregnancy

Female patients who become pregnant during the trial must stop study treatment immediately.

The Investigator must make every effort to try and ensure that a clinical trial patient or a partner of a clinical trial patient does not become pregnant during the trial or for six months afterwards. This should be done as part of the consent process by explaining clearly to the patient the potential dangers of becoming pregnant and also providing each patient with information about appropriate medically approved contraception. Two forms of medically approved contraception should be used, such as:

- oral contraceptives and condom;
- intra-uterine device (IUD) and condom;
- diaphragms with spermicidal gel and condom.

Contraception should be effective before the patient is enrolled on the trial, throughout the trial and for six months after completing the trial.

Alternatively, the patient may agree to sexual abstinence, effective from the first administration of IMP, throughout the trial and for six months afterwards. Abstinence is only considered to be an acceptable method of contraception when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

For male patients, it should be explained to the patient that if his partner is pregnant or breast-feeding when he is enrolled on the trial, the patient should use barrier method contraception (condom plus spermicidal gel) to prevent the unborn baby or the baby being exposed to MOv18 IgE.

However, if a patient or a partner of a patient does become pregnant, the reporting procedures below must be followed.

Any pregnancy occurring in a patient or a patient's partner during treatment with an IMP or occurring within six months of last IMP administration must be reported to the Pharmacovigilance Department within 24 hours of the site staff becoming aware of it using a Pregnancy Report Form (provided in the ITF). It is the Investigator's responsibility to obtain consent for follow-up from the patient or patient's partner. In addition, the Investigator must be made aware of the need to obtain contact details for the patient's partner's General Practitioner. The Pharmacovigilance Department will follow-up all pregnancies for the pregnancy outcome via the Investigator, using a Pregnancy Report Form.

The Investigator must ensure that all patients are aware at the start of a clinical trial of the importance of reporting all pregnancies (in themselves and their partners) that occur whilst being treated with the IMP and occurring up to six months after the last IMP administration. The Investigator should offer counselling to the patient and/or the partner, and discuss the risks of continuing with the pregnancy and the possible effects on the foetus. Monitoring of the patient should continue until the conclusion of the pregnancy, if the patient or patient's partner has consented to this. Monitoring of the baby should continue until 12 months after birth, if the patient or patient's partner has consented to this.

10 ASSESSMENT OF EFFICACY

10.1 Measurement of disease

Disease must be measured according to the RECIST 1.1 criteria given in Appendix 3.

Patients must have measurable disease or disease evaluable by assessment of tumour marker to be eligible for participation in the study (see Section 4.1). Previously irradiated lesions clearly progressing at the baseline disease assessment can be considered measurable disease.

10.2 Timing and type of tumour assessments

A thorough clinical and radiological evaluation of malignancy, as judged appropriate by the Investigator, and in line with the protocol, must be performed before starting the investigational medicinal product (IMP). The same methods that detect evaluable lesions at baseline must be used to follow these lesions throughout the study. To ensure compatibility, the radiological assessments used to assess response must be performed using identical techniques. Imaging based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumour effect of a treatment.

All radiological assessments and clinical measurements to assess response must be performed within 28 days before starting treatment. The interval between the last anti-cancer therapy and these measurements must be at least four weeks (28 days).

For this study, due to the limited duration of study treatment, complete (CR) and partial responses (PR) do not need to be confirmed by a subsequent assessment at least 4 weeks later. Stable disease criteria must be met at least once after study entry at a minimum interval of six weeks to be defined as stable disease (SD). Possible contribution of inflammatory cell infiltration to transient enlargement of tumours may be considered when assessing response and considering discontinuation of study treatment. Evaluation by tumour marker such as CA125 may be used for patients without measurable disease.

Copies of the scans must be available for external independent review if requested by the CDD.

10.2.1 Baseline evaluations

These must include radiological measurements of lesions in the chest and abdomen by CT scan or MRI scan and/or other radiological measurements as clinically indicated or clinical measurements as appropriate e.g. assessment of palpable lesions or measurement of tumour markers. All areas of disease present must be documented (even if specific lesions are not going to be followed for response) and the measurements of all measurable lesions must be recorded clearly on the scan reports. Any non-measurable lesions must be stated as being present. For clinical measurements, documentation by colour photography including a ruler to estimate the size of the lesion is strongly recommended, as this aids external independent review of responses. (See Appendix 3 Section 1.2.1 of RECIST criteria)

10.2.2 Evaluations during the study and at 'First Post-treatment Safety Assessment' 28 ±7 days after final dose)

Tumour assessments must be repeated every six weeks (i.e. after the first 6 doses during the Initial Dosing Period and again after 3 doses in the Maintenance Period) or more frequently, if clinically indicated. All lesions measured at baseline must be measured at every subsequent disease assessment and recorded clearly on the scan reports. All non-measurable lesions noted at baseline must be noted on the scan report as present or absent.

All patients, who are removed from the study for reasons other than progressive disease, must be re-evaluated at the time of treatment discontinuation, unless a tumour assessment was performed within the previous four weeks.

It is the responsibility of the Principal Investigator to ensure that the radiologists are aware of the requirement to follow-up and measure every target lesion mentioned at baseline and comment on the non-target lesions in accordance with RECIST criteria.

10.3 Tumour response

All patients who meet the eligibility criteria, receive at least one dose of study drug and have a baseline and at least one post-baseline assessment of disease will be evaluable for response. Patients who develop clear evidence of progressive disease (PD) without a formal disease assessment will be considered non-responders. There is no requirement for repeat assessments to be performed in order for a patient to be assigned a status of CR or PR in this study. To be assigned a status of stable disease (SD), tumour response measurements must have met the SD criteria at least once and at least six weeks after the first dose of the investigational medicinal product (IMP) MOv18 IgE is given.

Tumour response should be classified as “not evaluable” (NE), only when it is not possible to classify it under another response category, for example, when baseline and/or follow-up assessment is not performed or not performed appropriately.

Expert reviewers appointed by CDD may undertake an independent review of all the Investigator’s assessed objective responses (CR and PR). The expert reviewers will include at least one specialist who is not an Investigator in the study. The independent reviewer’s assessment will also be documented in the final clinical study report (CSR) along with the assessment made by the Investigator. The eCRF will reflect the Investigator’s opinion.

10.3.1 Recording of response in the eCRF

The applicable overall response category for each visit that includes disease assessment must be recorded in the eCRF.

10.3.2 Other definitions of outcome

Toxic death: Any death to which drug toxicity is thought to have a major contribution.

11 PATIENT WITHDRAWAL BEFORE COMPLETION OF TREATMENT

The Investigator must make every reasonable effort to keep each patient on study for the whole duration of the study (i.e. until 70 days ±14 days after last MOv18 IgE administration). However, if the Investigator removes a patient from the study or if the patient declines further participation, the Post-treatment Safety Assessments should ideally be performed before any subsequent therapeutic intervention. All the results of the evaluations and observations, together with a description of the reasons for withdrawal from the study, must be recorded in the medical records and in the eCRF.

Patients who are removed from the study due to adverse events (clinical or laboratory) will be treated and followed according to accepted medical practice. All pertinent information concerning the outcome of such treatment must be recorded in the eCRF and on the serious adverse event (SAE) report form where necessary.

The following are justifiable reasons for the Investigator to withdraw a patient from study:

- AE/SAE (including a positive skin prick test or anaphylaxis)
- Withdrawal of consent (note that a patient can withdraw consent to treatment but remain on study for follow-up of safety)
- Serious deviation of the study protocol (including persistent patient attendance failure and persistent non-compliance)
- Sponsor's decision to terminate the study
- Withdrawal by the Investigator for clinical reasons not related to the IMP (MOv18 IgE)
- Evidence of disease progression
- Pregnancy (for female patients during the study).

12 DEFINING THE END OF TRIAL

The ‘end of trial’ is defined as the date when the last patient has completed their final Post-treatment Safety Assessment or completed their final follow-up visit to assess ongoing drug-related AEs (whichever is later).

It is the responsibility of the CDD to inform the Medicines and Healthcare products Regulatory Agency (MHRA) and the Research Ethics Committee (REC) within 90 days of the ‘end of the trial’ that the trial has closed.

In cases of early termination of the study (for example, due to toxicity) or a temporary halt by the CDD, the CDD will notify the MHRA and the Main REC within 15 days of the decision and a detailed, written explanation for the termination/halt will be given.

The entire study will be stopped when:

- The drug is considered too toxic to continue treatment before the required number of patients have been recruited.

- The stated objectives of the study are achieved.

Regardless of the reason for termination, all data available for patients at the time of discontinuation of follow-up must be recorded in the eCRF. All reasons for discontinuation of treatment must be documented.

In terminating the study, CDD and the Investigators must ensure that adequate consideration is given to the protection of the patient’s interest.

13 DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

The final analysis will be conducted after one of the following conditions is met:

- The study is terminated early (for example, due to toxicity).
- All patients have had the opportunity to receive two cycles of treatment (six doses) and have completed their final Post-treatment Safety Assessment.

Once one of the conditions is met, a data cut-off date will be established. All patient visits occurring on or before this date will be analysed and summarised in the final clinical study report. Any data collected after this date will be summarised in a supplemental report.

13.1 Presentation of data

Data will be presented in a descriptive fashion. Variables will be analysed to determine whether the criteria for the study conduct are met. This will include a description of patients who did not meet all the eligibility criteria, an assessment of protocol deviations, IMP accountability and other data that impact on the general conduct of the study.

Baseline characteristics will be summarised for all enrolled patients. Patients who died or withdrew before treatment started or did not complete the required safety observations will be described and evaluated separately.

Treatment administration will be described for all cycles. Dose administration, dose modifications or delays and the duration of therapy will be described.

13.2 Safety

Safety data will be collected from the date of written consent. Safety variables will be summarised by descriptive statistics. Laboratory variables will be described using the NCI-CTCAE Version 4.02.

Adverse events (AEs) will be reported for each dose level and presented as summary tables presenting frequency of AEs by body system and by worst severity grade observed as well as total frequency of related and unrelated AEs. All patients who receive any amount of MOv18 IgE, either by IV infusion or as a skin prick test, will be evaluable for safety. However, dose escalation decisions require at least one or three patients (depending on the cohort) to receive 3 doses of IV MOv18 IgE without DLT (see Section 5.4).

13.3 Pharmacokinetics

Please refer to Table 6 in Section 8.3 for the timing of analyses of the PK assay.

Note that for patients in the lowest cohort at least, the dose of IV MOv18 IgE is so low that MOv18 IgE is expected to be undetectable on PK analysis.

The serum concentration/time data will be analysed using non-compartmental methods. The pharmacokinetic (PK) parameters to be determined for MOv18 IgE include the maximum observed plasma concentration (C_{max}), time to reach C_{max} (T_{max}), and the area under the plasma concentration time curve (AUC), and the terminal elimination half-life ($T_{1/2}$), mean residence time (MRT), total body clearance (CLT) and steady/state volume of distribution (V_{SS}).

13.4 Pharmacodynamics

Please refer to Table 6 in Section 8.3 for the timing of analyses of the Pharmacodynamic assays.

[redacted] No formal statistical analyses will be performed. The results of all pharmacodynamic assays will be reported and may be published but only those results available at the time of reporting will be included in the clinical study report.

13.5 Anti-tumour activity

Evaluating anti-tumour activity of MOv18 IgE is a secondary study objective. Eligible patients must receive at least one dose of the study drug to be evaluable for best overall response assessed according to RECIST version 1.1 (see Appendix 3). Best overall response will be presented in the data listings.

14 ADMINISTRATION

This study is conducted under a clinical trial authorisation (CTA) and approval from the Medicines and Healthcare products Regulatory Agency (MHRA) and the relevant Research Ethics Committee(s) will be obtained before the start of this study. This study is sponsored and managed by the Cancer Research UK, Centre for Drug Development (CDD). Applicable regulatory requirements are described in this section.

14.1 Protocol deviations and amendments

The protocol should be adhered to throughout the conduct of the study. If a situation arises where the conduct of the study may not be in line with the protocol, the site should discuss the suitable course of action with the CSM/CRA at the CDD.

A serious breach is a breach which is likely to effect to a significant degree: the safety or physical or mental integrity of the subjects of the trial, or the scientific value of the trial. In order that the Sponsor can fulfil their obligations in terms of reporting serious breaches of GCP to the MHRA within seven calendar days of identification, site staff must inform the Sponsor of any unplanned deviations to the trial protocol (or GCP principles) as soon as possible after the deviation occurs to allow prompt evaluation by the Sponsor.

Amendments to the protocol may only be made with the approval of the CDD. A protocol amendment may be subject to review by the assigned Ethics Committee, Health Research Authority (HRA) and the MHRA. Written documentation of the Ethics Committee and HRA (and if appropriate the MHRA) 'favourable opinion' (i.e. approval) must be received before the amendment can be implemented and incorporated into the protocol if necessary.

14.2 Completion of the electronic case report form (eCRF)

Electronic CRFs approved by the CDD will be used to collect the data. The Investigator is responsible for ensuring the accuracy, completeness, clarity and timeliness of the data reported in the eCRFs.

Only the Investigator and those personnel who have signed the Study Team Responsibilities Delegation Log provided by the CDD and have been authorised by the Investigator should enter or change data in the eCRFs. Authorised users will be included on a Master User List in order to be provided access to the eCRF. All protocol required investigations must be reported in the eCRF. The Investigators must retain all original reports, traces and images from these investigations for future reference.

Data will be entered directly into electronic screens by authorised site personnel. Amendments to eCRF data will be made directly to the system and the system audit trail will retain details of the original value(s), who made the change, a date and time, and a reason for the change.

Once an eCRF form has been entered by the site personnel, the data are cleaned using manual and automated checks. Queries will be issued electronically to the site. Authorised personnel must answer the queries by making relevant amendments to data or providing a response. Answered queries will be closed or reissued as appropriate.

Once the patient has completed their participation in the study and the eCRF has been fully completed, the Investigator must provide an electronic signature to authorise the complete subject casebook.

At the end of the study all eCRFs are retained and archived by the CDD and a PDF copy provided to the Investigator who is responsible for archiving at site.

14.3 Study performance and monitoring

Before the study can be initiated, the prerequisites for conducting the study must be clarified and the organisational preparations made with the study centre. CDD must be informed immediately of any change in the personnel involved in the conduct of the study.

During the study the CDD Clinical Research Associate (CRA) is responsible for monitoring data quality in accordance with CDD's standard operating procedures (SOPs). A strategic monitoring approach, including targeted source data verification, will be implemented where appropriate.

Before the study start, the Investigator will be advised of the anticipated frequency of the monitoring visits. The Investigator will receive reasonable notification before each monitoring visit.

It is the responsibility of the CRA to:

- review study records and compare them with source documents;
- check pharmacokinetic and pharmacodynamic samples and storage;
- discuss the conduct of the study and any emerging problems with the Investigator;
- check that the drug storage, dispensing and retrieval are reliable and appropriate; and
- verify that the investigational site facilities and staff remain acceptable.

It is the responsibility of the Sponsor to inform the Main REC within 90 days of the 'end of the trial' that the study has closed. (See definition in Section 12)

During the course of the trial, the Quality Assurance Department of the CDD, or external auditors contracted by the CDD, may conduct an on-site audit visit (ICH Topic E6 (R2) Guideline for Good Clinical Practice Sections 1.6).

Principal Investigators conducting this trial will accept the potential for inspection by the MHRA

14.4 Source document verification

Unless agreed in writing, all data collected in the eCRF must be verifiable by the source data. Therefore, it is the Investigator's responsibility to ensure that both he/she and his/her study team records all relevant data in the medical records. The Investigator must allow the CRA direct access to relevant source documentation for verification of data entered into the eCRF, taking into account data protection regulations. Entries in the eCRF will be compared with patients' medical records and the verification will be recorded in the eCRF and the monitoring report.

Some source data may exist only electronically and be entered, or loaded directly into the eCRF. The patients' medical records, and other relevant data, may also be reviewed by appropriate qualified personnel independent from the CDD appointed to audit the study, and by regulatory authorities. Details will remain confidential and patients' names will not be recorded outside the hospital.

14.5 Clinical study report

At appropriate intervals, interim data listings will be prepared to give the Investigators the opportunity to review the data and check the completeness of information collected. All clinical data will be presented at the end of the study on final data listings and summary tables. CDD will prepare a clinical study report based on the final data. The report will be submitted to the Investigator(s) for review and confirmation it accurately represents the data collected during the course of the study. Summary results of the trial will be provided by the CDD to the MHRA and to the Research Ethics Committee.

14.6 Record retention

During the clinical study and after study closure the Investigator must maintain adequate and accurate records to enable both the conduct of a clinical study and the quality of the data produced to be evaluated and verified. These essential documents (as detailed in Chapter V of Volume 10 (Clinical Trials) of The Rules Governing Medicinal Products in the European Union based upon Section 9 of the ICH GCP Guidelines), including source documents such as scans, study related documents and copies of the eCRFs, associated audit trail and serious adverse event (SAE) report forms, shall show whether the Investigator has complied with the principles and guidelines of Good Clinical Practice (GCP).

All essential documents required to be held by the Investigator must be stored in such a way that ensures that they are readily available, upon request, to the Regulatory Agency or Sponsor, for the minimum period required by national legislation or for longer if needed by the CDD. Records must not be destroyed without prior written approval from the CDD.

The medical files of study subjects shall be retained in accordance with national legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

14.7 Ethical considerations

Before starting the study, the protocol, patient information sheets and consent forms will go through the CDD's independent peer review and PSRB review process, and receive the favourable opinion of the Research Ethics Committee.

It is the Chief/Principal Investigator's responsibility to update patients (or their authorised representatives, if applicable) whenever new information (in nature or severity) becomes available that might affect the patient's willingness to continue in the study. The Chief/Principal Investigator must ensure this is documented in the patient's medical notes and the patient is re-consented.

The Sponsor and Chief/Principal Investigator must ensure that the study is carried out in accordance with the GCP principles and requirements of the UK Clinical Trials regulations (SI 2004/1031 and SI 2006/1928 as amended), the ICH GCP guidelines and the Declaration of Helsinki (Appendix 2).

14.8 Indemnity

This study is being carried out under the auspices of Cancer Research UK and therefore injury to a patient caused by the compounds under study will not carry with it the right to seek compensation from the pharmaceutical industry. Cancer Research UK will provide patients with compensation for adverse side effects, in accordance with the principles set out in the Association of the British Pharmaceutical Industry (ABPI) guidelines on compensation for medicine-induced injury.

14.9 Publication policy and press releases

Results of this study must be submitted for publication. The CDD must be involved in reviewing all drafts of the manuscripts, abstracts, press releases and any other publications. Manuscripts must be submitted to the CDD at least 28 days in advance of being submitted for publication to allow time for CDD to schedule a review and resolve any outstanding issues. Abstracts and press releases must be submitted to the CDD at least 14 days in advance of being released. Authors must acknowledge that the study was sponsored by and performed with the support of the CDD.

The contribution of the CDD should be recognised by at least one member of staff being included as an author on the publication. The Biotherapeutics Development Unit (BDU) have developed and manufactured MOv18 IgE and so a member of the BDU staff should be included as an author.

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16 APPENDICES

16.1 Appendix 1: WHO Performance Scale

WHO Performance Status	Score
Fully active, able to carry out all normal activity without restriction.	0
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light housework, office work.	1
Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	2
Capable of only limited self-care. Confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair.	4

16.2 Appendix 2: Declaration Of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects**,** including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.
16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician
17. or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.
18. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
19. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
20. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.
21. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
22. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
23. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

25. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
26. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.
27. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.
28. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
29. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.
31. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

32. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

    - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
    - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

34. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

35. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

36. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

16.3 Appendix 3: Assessment of Disease Response

Assessment of disease response in this study should be performed according to RECIST criteria, as summarised below. Investigators may choose to limit the number of target lesions to only 5, or they may analyze more target lesions than the RECIST 1.1 formalism allows, without a specific limitation on the number of target lesions per organ.

New response evaluation criteria in solid tumours (RECIST criteria):

Revised RECIST guideline (version 1.1)

E.A. Eisenhauer *et al*. (2009) *European Journal of Cancer* **45:** 228-247

Note that this is an abridged version of the RECIST criteria. Please refer to the above article for detailed appendices and if in doubt.

1. Measurability of tumour at baseline

1.1 Definitions

At baseline, tumour lesions/lymph nodes will be categorised measurable or non-measurable as follows:

1.1.1 Measurable

Tumour lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10mm by CT scan (CT scan slice thickness no greater than 5 mm; see Appendix II on imaging guidance).
- 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be >15mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also notes below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

1.1.2 Non-measurable

All other lesions, including small lesions (longest diameter <10mm or pathological lymph nodes with ≥10 to <15mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

1.1.3. Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

1.2. Specifications by methods of measurements

1.2.1. Measurement of lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

1.2.2. Method of assessment

The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions:

Clinical lesions will only be considered measurable when they are superficial and ≥10mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray:

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI:

CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). More details concerning the use of both CT and MRI for assessment of objective tumour response evaluation are provided in the publication from Eisenhauer et al.

Ultrasound:

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next (described in greater detail in Appendix II). If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy:

The utilisation of these techniques for objective tumour evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumour markers:

Tumour markers alone cannot be used to assess objective tumour response. If markers are initially above the upper normal limit, however, they must normalise for a patient to be considered in complete response.

Cytology, histology:

These techniques can be used to differentiate between PR and CR in rare cases (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain).

2. Tumour response evaluation

2.1 Assessment of overall tumour burden and measurable disease

To assess objective response or future progression, it is necessary to estimate the overall tumour burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion (as detailed above in Section 1).

2.2. Baseline documentation of ‘target’ and ‘non-target’ lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded). For evidence to support the selection of only five target lesions, see analyses on a large prospective database in the article by Bogaerts *et al*. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. An example is provided in Fig. 3 of Appendix II of the publication by Eisenhauer et al.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumour. Pathological nodes which are defined as measurable and may be identified as target lesions, must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumour. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non- pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterise any objective tumour regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

2.3. Response criteria

2.3.1. Evaluation of target lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

2.3.2. Special notes on the assessment of target lesions

Lymph nodes.

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure'.

While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment:

When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

2.3.3. Evaluation of non-target lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

2.3.4. Special notes on assessment of progression of non-target disease

The concept of progression of non-target disease requires additional explanation as follows:

When the patient also has measurable disease.

In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease.

This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance

there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumour burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localised to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be substantial.

2.3.5. New lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable.

to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up:

- If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
- If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.
- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

2.4 Evaluation of best overall response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation (not required in this trial). Should a response not be documented until after the end of therapy in this trial, post-treatment assessment may be considered in determination of best overall response as long as no alternative anti-cancer therapy has been given. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

2.4.1. Time point response

It is assumed that at each protocol-specified time point, a response assessment occurs. Table 1 on the next page provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

2.4.2. Missing assessments and not evaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

2.4.3. Best overall response: all time points

The best overall response is determined once all the data for the patient is known.

Best response in these trials (in which confirmation of complete or partial response is NOT required): is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable. A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

Table 1 – Time point response: patients with target (+/–non-target) disease

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

Table 2 – Time point response: patients with non-target disease only

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD(a) NE
Not all evaluated	No	PD
Unequivocal PD	Yes or No	PD
Any	Yes	

CR = complete response, PD = progressive disease, and NE = inevaluable.

(a) 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

2.4.4. Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables 1 and 2.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring.

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next

scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

2.6.2. Duration of overall response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

2.6.3. Duration of stable disease

Stable disease is measured from the start of the treatment (in randomised trials, from date of randomisation) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

16.4 Appendix 4: Treatment of Anaphylaxis

[Based on (Simons et al., 2011a; Simons et al., 2011b)]

If the patient experiences symptoms suggestive of an infusion-related reaction or cytokine release, the infusion must be slowed or interrupted, and the patient must be treated with oxygen, paracetamol, antihistamines, fluid resuscitation and/or steroids, as clinically indicated.

Anaphylaxis should be suspected if:

- There is a sudden onset and rapid progression of symptoms
- The reaction is > Grade 2 in severity (see Appendix 5) and fails to respond to the conservative measures outlined above

or

- The reaction is > Grade 2 in severity and associated with rapid onset of urticaria (within 10 minutes of starting the infusion).
- The patient experiences life-threatening airway and/or breathing and/or circulation problems

If anaphylaxis is suspected based on these criteria:

- Summon help (resuscitation team)
- Stop the infusion
- Inject epinephrine (adrenaline) intramuscularly into the mid-anterolateral aspect of the thigh
    - 0.5-1mL 1:1000 epinephrine
    - Record the time of dose and repeat it in 5-15 minutes if needed (e.g. because of progressing hypotension and/or laryngeal oedema).
- Place the patient on his/her back or in a position of comfort if there is respiratory distress and/or vomiting; elevate the legs
- If not already started, give high-flow (6-8 L/min) supplemental oxygen by face mask
- If not already started, give 1-2 litres of 0.9% isotonic saline rapidly (e.g. 5-10 mL/kg in the first 5-10 minutes), as clinically indicated
- Give chlorphenamine 10mg IM or slow IV
- Consider hydrocortisone 200mg IM or slow IV
- Consider bronchodilators if clinically indicated.

Cardiac arrest associated with anaphylaxis

- If indicated, perform cardiopulmonary resuscitation as per Adult Life Support guidelines

The possibility of early recurrence of symptoms following the initial episode should always be considered. In patients requiring treatment with epinephrine, chlorphenamine and corticosteroids should be continued for 24 hours (total) to minimise the possibility of a ‘late reaction’ (which sometimes occurs 4-6 hours after an anaphylactic episode). In the event of recurrence or other evidence that residual MOv18 IgE could be contributing to an ongoing systemic reaction, the use of omalizumab should be considered. Omalizumab is a monoclonal antibody licensed and NICE-approved for severe persistent allergic asthma; it acts by binding to the Fc domain of IgE and preventing binding to both FcαRI and FcαRII.

16.5 Appendix 5: Trial-specific Grading of IgE-associated Mast Cell Degranulation (anaphylaxis)

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
No infusion-related symptoms or mild symptoms not requiring treatment, in the presence of a positive serum tryptase assay	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g. antihistamines, NSAIDS, IV fluids), in the presence of a positive serum tryptase assay	Prolonged and/or severe symptoms with hypotension (systolic BP < 100 mmHg) and/or angioedema, laryngeal oedema, bronchospasm or hypoxia* (sats <92% on room air), in the presence of a positive serum tryptase assay	Life-threatening consequences (pressor or ventilatory support indicated), in the presence of a positive serum tryptase assay	Death
** - for patients with lung metastases whose baseline saturations on air may be significantly lower than 100%, hypoxia is defined as a drop in saturations requiring the administration of oxygen* In general, rapid onset of urticaria suggests mast cell degranulation (anaphylaxis) rather than cytokine release syndrome. However, urticaria alone appears to be a common but manageable symptom of MOv18 IgE infusion.				

Note: for this study, a positive serum tryptase assay is required for infusion-related events to be ascribed to IgE-associated mast cell degranulation (anaphylaxis).

16.6 Appendix 6: NCI-CTCAE v.4.02 Grading of Cytokine Release Syndrome

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g. antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 h	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g. renal impairment, pulmonary infiltrates)	Life-threatening consequences; pressor or ventilatory support indicated	Death
Cytokine release syndrome definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and shortness of breath; it is caused by the release of cytokines from the cells.					

Note: for this study, a negative serum tryptase assay is required for an infusion-related event to be ascribed to cytokine release syndrome

16.7 Appendix 7: Levels of Asthma Control (GINA Guidelines 2012[$])

A. Assessment of current clinical control (preferably over 4 weeks)			
Characteristic	**Controlled (all of the following)**	**Partly controlled (any measure present)**	**Uncontrolled**
Daytime symptoms	None (twice or less/week)	More than twice/week	Three or more features of partly controlled asthma*†
Limitation of activities	None	Any	
Nocturnal symptoms/awakening	None	Any	
Need for reliever/rescue treatment	None (twice or less/week)	More than twice/week	
Lung function (PEF or FEV_1) ‡	Normal	<80% predicted or personal best (if known)	
B. Assessment of future Risk (risk of exacerbations, instability, rapid decline in lung function, side effects)			
Features that are associated with increased risk of adverse events in the future include: Poor clinical control, frequent exacerbations in past year*, ever admission to critical care for asthma, low FEV_1, exposure to cigarette smoke, high dose medications			

[$] (Global Strategy for Asthma Management and Prevention, 2012)

*Any exacerbation should prompt review of maintenance treatment to ensure that it is adequate

† By definition, an exacerbation in any week makes that an uncontrolled asthma week

‡ Without administration of a bronchodilator

N.B. Patients with current uncontrolled asthma (according to Part A above) or at high future risk (indicated by at least one of the criteria listed in Part B above, other than exposure to cigarette smoke and use of high dose medications) are not eligible for the study.

16.8 Appendix 8: Skin Prick testing to evaluate sensitivity to MOv18 IgE

Skin prick testing will be performed and the response assessed at 15, 30 and 60 mins post skin prick test initiation, before each administration of IV MOv18 IgE solution. Testing for sensitivity to MOv18 IgE will include a negative saline control and a positive histamine control to verify that the patient's skin is normally responsive.

Essential safety equipment:

Always have an emergency kit available in or close to the clinic room. This must include:

- Oxygen
- Injectable Epinephrine (Adrenaline) B.P. 1:1,000 (1mg/mL)
- Hydrocortisone cream
- Oral Prednisolone
- IV hydrocortisone
- Oral antihistamines e.g. cetirizine, chlorpheniramine
- IV chlorphenamine
- Inhaled bronchodilator e.g. salbutamol
- Nebuliser masks

Method

The following method is based on the standard operating procedure on how to perform adult skin prick testing from the BSACI Nurses in Allergy Committee (Kathryn Powrie 15.10.2015 final v7): http://www.bsaci.org/Guidelines/SOPs. Minor deviations from these methods are allowed if agreed in writing by the sponsor and they are according to local SOPs and practice".

Skin prick testing is a method used to determine the presence of specific IgE. Skin prick testing should only be interpreted in conjunction with a clinical history as a positive skin prick test alone is not diagnostic of clinical disease [1,2]. Depending on the allergen, approximately half of positive tests occur in patients who are not allergic to that allergen. Skin prick testing should be performed by an appropriately trained and competent healthcare worker who is also trained in recognition and treatment of anaphylaxis [3].

Exclusions

Skin prick test reactions are inhibited by antihistamines and may be inhibited by tricyclic antidepressants, topical corticosteroids and UV light treatment. Therefore, where possible inhibitory medication should be stopped or alternative testing methods considered [1,2]. Anti-histamines should be stopped prior to testing (see Protocol Sections 4.1.2 and 5.7).

Cautions

Caution should be taken when considering skin prick testing in pregnancy, for patients with unstable asthma or those taking beta blockers and/or ACE inhibitors[1,2].

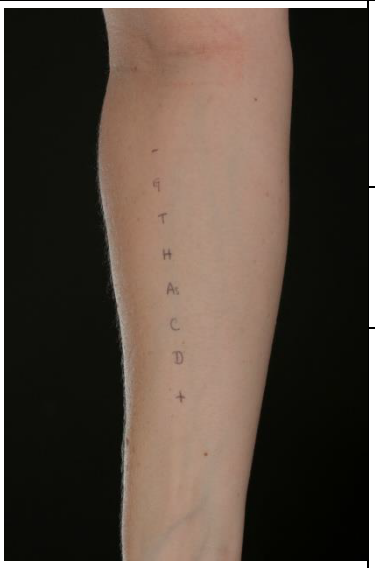
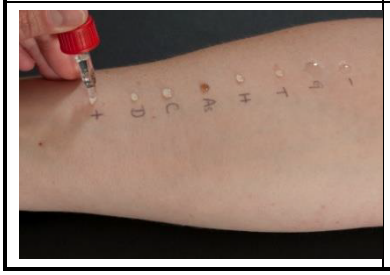
Equipment

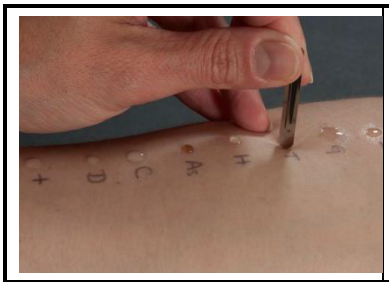
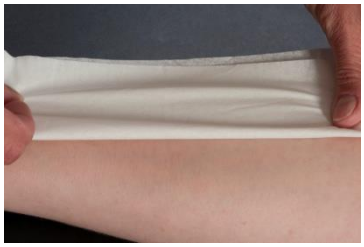
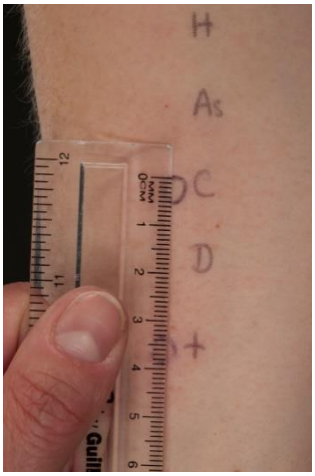
- MOv18 IgE solution for skin prick testing, and positive and negative control solutions (stored at +2-+8°C). Check expiry date and date opened (some manufacturers state that skin test solutions should be used within 6 months of opening.) [4]
- Pen
- Individual sterile skin prick testing lancets

- Sharps bin
- Tissues
- Skin test measure/ruler
- Timer / clock / watch
- Essential safety equipment (see above) including adrenaline 1:1000 [5]

Preparation

Verbal consent for the procedure should be obtained. The procedure should be undertaken in accordance with local infection control policy using appropriate hand hygiene measures. Select appropriate test site free from eczema / dermatitis, the preferred site is the forearm but the back may also be used.

	PROCEDURE [1,2,3,6]	**RATIONALE**
	Ensure test site is free from body lotion and moisturisers	Body lotion / moisturiser can cause allergen drops to run, causing cross contamination.
	Test site should be hygienically clean but does not need to be not be cleaned with alcohol or antiseptic	
	Ensure patient is in a comfortable position sitting or, if needle phobic, lying down. Rest arm on a level surface, using pillow if necessary.	To ensure patient is relaxed and able to remain still during the test.
	Mark the test sites approximately 2.5cm apart, using first letter of allergen being tested. Avoid the skin creases (elbow and wrist)	To ensure any reactions do not overlap so that accurate measurements can be made.
	Begin with the negative control and end with the positive control	To provide consistency, to prevent cross contamination from the histamine control and for patient comfort because the histamine control reaction time is the quickest.
	Place one drop of each selected allergen solution* next to relevant marked site. *for prick to prick testing see additional guidance below.	To ensure accurate identification of the allergen when results are read

	Using gentle pressure, push the lancet through allergen solution and into the surface layer of the skin at a 90^{O} angle.	To ensure that the allergen penetrates the outer surface of the skin. To reduce risk of causing bleeding. To ensure a standardised test
	Discard lancet into sharps bin	To ensure safe disposal of sharps
	Repeat the procedure for each allergen and the controls using a new lancet each time	To prevent cross contamination of the allergens
	Remove surplus allergen by blotting test sites with tissue ensuring that there is no cross contamination between test sites.	To remove excess allergen solution and prevent cross contamination of test sites.
	Advise patients not to scratch the test sites whilst waiting for the results to develop	To allow for accurate reading of results.
	Advise patients to report promptly any systemic adverse reaction	To ensure prompt treatment of any adverse reaction
	Results should be read at 15, 30 and 60 minutes after the test. Measure the wheal diameter in mm. For asymmetric wheals measure the longest extent of the wheal in mm and the extent 90^{o} to the first measurement (eg 3x3mm). An imprint of the result can also be made by drawing round the wheal in pen and taking a print using skin tape which can then be stuck onto the results sheet. The flare may also be recorded.	To ensure accurate assessment of the reaction is recorded.

	Any pseudopodia should be noted but not included in the measurement of the wheal	
	A wheal diameter of more than 3mm larger than the negative control is a positive reaction	
	A wheal response to the negative control indicates dermographism	Document the response to the negative control. Interpretation of other positive results must allow for subtraction of the negative control. The need for further, alternative testing should be considered by the clinician who has requested the test.
	Absence of a wheal at the positive control suggests that a topical or oral medication with antihistaminic properties may have been taken. Repeat the positive control and if still negative record as an invalid test.	Document that the positive control has not reacted. Either repeat the skin tests off anti-histamines /other medication or the requesting clinician can consider specific IgE serology.
	Advise the patient that the wheals will fade, usually within an hour.	To inform the patient
	Topical 1% hydrocortisone, oral anti-histamines or a cold compress may be given to relieve severe itch in line with a prescription.	To enhance patient comfort and relieve severe itch
	Record the outcome of the test in the patient's notes including; • date of test • patient name, date of birth and hospital number • skin prick test method • wheal size in mm • any recent antihistamine medication with date/time of last dose. • If a positive response is observed, the time point of the response should be recorded i.e. 15, 30 or 60 min assessment point. • name, designation and signature of person performing the skin prick test	Ensure accurate documentation. To note: If the skin prick test is positive at ANY of the three time points, that will constitute a positive result.

References

1 The skin prick test – European Standards Clinical and Translational Allergy 3:3 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3565910/

2 Bousquet et al (2012) Practical guide to skin prick tests in allergy to aeroallergens Allergy 67: 18-24

http://onlinelibrary.wiley.com/doi/10.1111/j.1398-9995.2011.02728.x/pdf [accessed 16.01.2015]

3 Fitzsimons R et al (2014) Allergy Nurse Competency Document BSACI http://www.bsaci.org/professionals/nurses-specialising-in-allergies [accessed 16.01.2015]

4 Summary of product characteristics Soluprick Timothy Grass ALK Abello http://www.alk- abello.com /UK/products/soluprickSQ/Lists/Soluprick%20SQ/Timothy%20Grass%20SmPC.pdf [accessed 15.10.2015]

5 UK Resuscitation Council (2008) Emergency Treatment of Anaphylactic Reactions https://www.resus.org.uk/search/?q=anaphylaxis

6 King et al (2010) Paediatric Skin Prick Testing SOP BSACI http://www.bsaci.org/Guidelines/Skin_Prick_Testing.pdf [accessed 16.01.2015]