Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 1

Extract from the Clinical Evaluation Report for Remestemcel-L, *ex vivo* adult human mesenchymal stem cells

Proprietary Product Name: Prochymal

Sponsor: Delpharm Consultants Pty Limited

First round CER: 3 January 2012

Second round CER: 28 June 2012

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

1. List of abbreviations commonly used in this CER

Abbreviation	Meaning
aGvHD	acute Graft versus Host Disease
BMA	Bone Marrow Aspirate
BMMNCs	Bone Marrow Mononuclear cells
bMSCs	baboon MSCs
BSA	Bovine Serum Albumin
cMSCs	canine MSCs
CR	complete response
DCB	Donor Cell Bank
DCs	Dendritic Cells
DLI	donor leukocyte infusions
DMEM	Dulbecco's Modified Eagle Medium
DMSO	dimethyl sulfoxide
DP	Drug Product
DS	Drug Substance
ECG	electrocardiogram
ELISA	Enzyme Linked Immuno Sorbent Assay
FBS	Foetal Bovine Serum
GFP	Green Fluorescent Protein
GvHD	Graft versus Host Disease
HCT	haematopoietic cell transplantation
HLA	human leukocyte antigen
hMSCs	human mesenchymal stem cells
hPBMCs	human peripheral blood mononuclear cells
HSA	human serum albumin

Abbreviation	Meaning
HSCT	haematopoietic stem cell transplantation
IA	intra artery
IDO	indoleamine 2,3 dioxygenase
IFN-γ	interferon gamma
IM	intramuscular
IP	intraperitoneal
ISCT	International Society for Cellular Therapies
ITT	Intention To Treat
IV	intravenous
KGF	keratinocyte growth factor
KLH	Keyhole Limpet Hemocyanin
mcMSCs	macaque MSCs
mITT	modified Intention To Treat
MLRs	Mixed Lymphocyte Reactions
mMSCcm	mMSC conditioned media
MSCs	mesenchymal stem cells
NCP	New Cytomate Product
Neor	neomycin resistance gene
NK	Natural Killer
NO	Nitric Oxide
NOAEL	No Observed Adverse Effect Level
OR	overall response
PBLs	Peripheral Blood Leukocytes
PCR	Polymerase Chain Reaction
PD	pharmacodynamics

Abbreviation	Meaning
PHA	phytohemagglutinin
PK	pharmacokinetics
PP	Per Protocol
PR	partial response
rMSCs	rat MSCs
SAE	serious adverse event
SC	Subcutaneous
SCP	Standard Centrifuged Product
sMSCs	swine MSCs
SOC	System Organ Class
TBI	total body irradiated
TEAE	treatment emergent adverse event
TNF-α	tumour necrosis factor-α
TSE	Transmissible Spongiform Encephalopathy
UEDs	Unanticipated Early Deaths
VEGF	vascular endothelial growth factor

2. Clinical rationale

The clinical rationale for the development of Prochymal is outlined in Module 2 of the submission (Clinical Overview and Clinical Summary of Efficacy), and in the sponsor's letter of application to register Prochymal for the proposed indication. The main features of the submitted clinical rationale are outlined below.

Acute graft versus host disease (GVHD) is an iatrogenic, progressive and lethal complication of haematopoietic stem cell transplantation (HSCT) and donor leukocyte infusions (DLI). In acute GVHD, donor T-cells recognise non-self antigens on the recipient tissues and interact with these antigens resulting in inflammation and host tissue destruction. The postulated pathophysiology of acute GVHD is based on a sequential three phase model: (1) injury to the host environment resulting in release of cytokines ('cytokine storm'); (2) donor T-cell activation, proliferation, and differentiation; and (3) organ cell damage caused by direct cytotoxicity or through the production of inflammatory cytokines (Ferrara et al., 1999; Teshima and Ferrara, 2002; Devetten and Vose, 2004).

Clinical GVHD has acute and chronic forms. Traditionally, the acute form has been distinguished from the chronic form by the time of onset after haematopoietic cell transplantation (HCT): i.e., acute GVHD occurring within 100 days, and chronic GVHD occurring beyond 100 days even if the manifestations of chronic disease could not be distinguished from acute disease (Deeg, 2007; Vigorito et al., 2009). However, current consensus opinion is that acute and chronic GVHD should be distinguished by clinical characteristics rather than time after transplantation (Filipovich et al., 2005; Vigorito et al., 2009). Classic acute GVHD is characterised by clinical features relating to the skin (maculopapular rash), gastrointestinal tract (predominantly diarrhoea) and liver (cholestatic jaundice), and occurs within 100 days of HCT or DLI (Shlomchik, 2007; Vigorito et al., 2009).

In a review of therapy in 740 patients with acute GVHD, Martin et al (1990) found that at the beginning of treatment 81% had rash, 54% had gastrointestinal involvement and 50% had liver dysfunction. In addition to classic acute GVHD, the broad category of acute GVHD also now includes persistent, recurrent or late-onset disease occurring more than 100 days after HCT or DLI (Vigorito et al., 2009). In contrast to acute GVHD, chronic GVHD has more diverse clinical features and can often resemble autoimmune syndromes (Shlomchik, 2007; Vigorito et al., 2009). The clinical features of acute GVHD in children are similar to those in adults, and there appear to be no significant differences between paediatric and adult patients in the clinical symptoms and the pathophysiology of the disease (Goker et al, 2001; MacMillan et al, 2002a; Jacobsohn, 2007). Data from a recent meta-analysis of steroid refractory acute GVHD in adults and children treated with MSCs suggests that children might respond better to treatment than adults (Wernicke et al., 2011).

The incidence and severity of acute GVHD is determined by the extent of involvement of the three primary organs affected by the disease (i.e., skin, gastrointestinal tract and liver). The history of the Consensus grading system for acute GVHD as originally proposed by Glucksberg et al (1974), and subsequently revised by Thomas et al (1975), is outlined by Rowlings et al (1997). This system involves initial staging of skin, liver and gut involvement by severity of clinical signs, followed by grading based on the pattern and severity of organ involvement and subjective clinical assessment of the disease into grades I (mild), II (moderate), III (severe) and IV (very severe). During the development of Prochymal, grading of acute GVHD changed from the older Consensus grading system (Grades I-IV), to the more recent International Bone Marrow Transplant Registry (IBMTR) grading system (Grades A-D). Therefore, some patients who participated in early Prochymal clinical trials were assessed using the Consensus grading system. Consequently, for the purposes of evaluation, Osiris considers that Consensus Grades I-IV correspond to IBMTR Grades A-D. The criteria for the IBMTR Severity Index for acute GVHD can be found in Rowlings et al (1997).

There are a number of risk factors that have been identified as having a role in the induction of acute GHVD. Goker et al (2001) consider histo-incompatability as the most important risk factor, but also note other risk factors including conditioning regimens with either high dose total body irradiation or high dose chemotherapy, the lack of a sterile microenvironment including the absence of gut decontamination, advanced recipient and donor age, gender mismatching (e.g., female multiparous donors for male recipients), underlying primary disease (e.g., leukemia, particularly CML), state of primary donor alloimunisation (e.g., multiple transfusions), prior splenectomy, viral infection, source of stem cell and graft cell composition, and type of prophylaxis.

There are no approved treatments for acute GVHD, and survival in patients with acute GVHD depends on the severity of the disease (Przepiorka et al., 1995). While there are no approved treatment for acute GVHD, corticosteroids are generally used as first line therapy and if patients do not adequately respond to these agents then mortality is high (Wolf et al., 2011). Patients with the most severe forms of acute GVHD not responding to corticosteroid therapy have expected one-year survival rates of 5% to 30% (Deeg, 2007; MacMillan 2002b; Martin, 1990; Przepiorka, 1995; Weisdorf, 1990). In patients refractory to first-line treatment with systemic corticosteroids, immunosuppressive agents are generally employed as second-line treatment despite limited evidence of efficacy and the known risks associated with these drugs.

Comment: The clinical rationale supporting the development of Prochymal is considered to be acceptable. There is a recognised unmet clinical need for efficacious and safe agents for the treatment of acute GVHD refractory to treatment with corticosteroids and other immunosuppressive agents.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The clinical dossier included two clinical efficacy and safety studies supporting the proposed indication, but no pharmacokinetic (PK) or pharmacodynamic (PD) studies in humans.

The submission included the following clinical information:

- 1 Phase III study in 260 adult and paediatric patients [Protocol 280]; 1 statistical analysis of the paediatric subpopulation (n=28) enrolled in Protocol 280; 1 expanded access study in 59 paediatric patients [Protocol 275]; single use reports of Prochymal in 12 patients; 2 cardiac safety synopses [reports 401 and 402]; case report forms (CRFs) and individual patient listings for studies 280 and 275, and single patient use CRFs; literature references.

The clinical data was provided in CTD format and included hard and electronic (DVD) copies. The sponsor provided an assurance that the hard and electronic copies of the submission were identical in content (except for IPD which were only presented electronically). The DVD was comprehensive and facilitated the evaluation of the submission.

> **Comment:** The submitted clinical data set included 260 patients (including 28 paediatric) from Protocol 280, 59 paediatric patients from Protocol 275, and 12 paediatric patients from the report of single-patient, emergency-use protocols approved by the FDA. The Module 2 clinical overview, and summaries of clinical efficacy and safety reviewed only the submitted paediatric data (i.e., study 275; and paediatric subgroup from study 280). This suggests that the submission was primarily prepared by Osiris to support Prochymal as rescue treatment for acute GVHD in a paediatric population (i.e., patients < 18 years of age).
>
> Data from Protocol 275 for all patients who completed the study by 30 December 2009 (n=59) is identified in the Clinical Overview (Module 2.5) as forming the 'pivotal data

set' in the submission. Similarly, the Summary of Clinical Efficacy (Module 2.7.3) identifies Protocol 275 as the pivotal study for 'evaluation of Prochymal treatment effectiveness' with Protocol 280 providing 'corroborative evidence'. However, in this clinical evaluation report (CER), Protocol 280 is considered to be the pivotal study and Protocol 275 is considered to be the supportive study. The reasons for Protocol 275 being considered to be supportive rather than pivotal for the Australian submission include: the open-label, single-arm (Prochymal) design; the absence of a placebo arm; and the inclusion of only paediatric patients (2 years to 17 years of age, inclusive) while the proposed indication includes patients aged ≥ 6 months without an upper age limit. The reasons for Protocol 280 being considered to be the pivotal study for the Australian submission include: Phase III, randomised, placebo-controlled, and double-blind in design; and inclusion of patients aged 6 months to 70 years, inclusive, which is consistent with the population included in the proposed indication.

The Clinical Overview (Module 2.5) states that '[d]uring the enrollment phase of Protocol 280, Osiris continued to receive numerous requests from physicians participating in [the study] to treat paediatric patients with Prochymal, as they did not want to enroll patients with life-threatening disease into a trial with the chance of randomization to placebo'. This statement demonstrates the difficulty of undertaking formal placebo-controlled clinical trials in life-threatening orphan diseases, particularly in a paediatric population, even when the clinical efficacy and safety of the administered product has not been adequately demonstrated. In any event, as a 'result of these requests the US [FDA] approved a single-arm study designed for Prochymal to treat refractory aGVHD in patients aged less than 18 years of age (Protocol 275)'. The clinical overview also comments that '[w]hile limiting the number of pediatric patients with direct placebo comparators, the decision to make open-label Prochymal available appeared to benefit the children treated and likely saved lives'. The clinical overview also states that 'pediatric enrollment in this program [Protocol 280] was ultimately curtailed due to ethical concerns raised by some investigators. These focused on entering pediatric patients suffering from an immediately life-threatening condition into a trial with a placebo arm, despite the concomitant use of the institutional second-line therapy in all patients'. However, while noting the comments in the clinical overview it should be emphasised that Protocol 280 (randomised, placebo-controlled, double-blind) was approved for children and adults by independent ethics committees and/or independent review boards at 72 sites in the 7 countries in which the study was undertaken (i.e., United States, Canada, Australia, Germany, Italy, Spain, and the United Kingdom), and was stated to have been conducted in accordance with Good Clinical Practice and the Declaration of Helsinki.

The sponsor provided a justification (Module 1.11.2) for not submitting biopharmaceutical studies. This justification addressed the issues listed in Part 4, Appendix 15 of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM, June 2004). The sponsor anticipates that while Prochymal (a suspension of cells for iv injection) is not a simple solution, bioavailability is expected to be complete. It is considered that this is reasonable assumption. The submission included no PK or PD studies in humans. The sponsor acknowledges that the PK studies for Prochymal were limited to tissue distribution studies in animals. The relevant TGA adopted guidelines (Guideline on Human Cell Based Medicinal Product EMEA/CHMP/410869/2006) discuss various approaches to studying the PDs and PKs of cell based medicinal products and notes that alternative approaches to standard methods might be required for these products.

3.2. Paediatric data

The submission includes data from studies undertaken in both paediatric and adult patients with refractory acute GVHD. Osiris states that paediatric subjects have been a part of the Prochymal clinical development plan since its inception. Consequently, a separate clinical development plan for paediatric patients has not been required. Protocol 275 included paediatric patients (n=59) only and Protocol 280 (paediatric and adult population) included a subgroup analysis of paediatric patients (n=28). Based on the contents of the Clinical Overview [Module 2.5] and the Summaries of Clinical Efficacy [Module 2.7.3] and Safety [Module 2.7.4] it appears that the submission has been prepared to support a paediatric indication only, rather than a paediatric and adult indication.

3.3. Good clinical practice

The studies in the submission sponsored by Osiris are stated to have been 'completed according to the guidelines of Good Clinical Practice including the archiving of essential documents. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial patients are protected, consistent with the principles that have their origin in the Declaration of Helsinki'.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

There were no Prochymal pharmacokinetic data in humans in the submission. Pharmacokinetic studies for Prochymal are limited to tissue distribution studies in animals. Osiris states that suitable techniques are not currently available to measure the distribution of hMSCs in patients with GVHD. Preclinical studies are stated to have demonstrated that hMSCs clear from the blood within hours of administration. The cells initially distribute to the lungs within minutes of infusion, and at 24 hours post-infusion a majority of the cells are found in the lungs with lesser amounts in the liver.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

There were no Prochymal pharmacodynamic data in humans in the submission. The pharmacodynamics of Prochymal have been studied only in animals. Osiris states that there are no techniques currently available to measure the pharmacodynamics of Procyhmal in humans. Consequently, the effects of Prochymal in humans are assessed through clinical outcomes.

6. Dosage selection for the pivotal studies

Initial studies with MSCs reported promising results in paediatric and adult patients with steroid-refractory grade III or IV acute GVHD (Le Blanc et al., 2004; Le Blanc et al., 2005; Le Blanc and Ringden 2006). In 16 patients (14 acute and 2 chronic GVHD) described by Le Blanc et al (2005), the median dose was 1 x 10^6 cells/kg (range 0.4 to 9 x 10^6 cells/kg), with the dose being administered from 1 to 3 times (9 patients received 1 dose, 6 patients received 2 doses, and 1 patient received 3 doses).

Based on the encouraging results from the initial studies with MSCs in acute GVHD, Osiris undertook an open-label, Phase II study in adults aged 18 to 70 years (inclusive) with adult GVHD (Grade II-IV) to determine whether the addition of Prochymal at a dose of 2 or 8 x 10^6 MSCs/kg to corticosteroid therapy would improve patient outcomes (Kebriaei et al., 2009). Two infusions of Prochymal were administered, with the first being given 24 to 48 hours after the diagnosis of acute GVHD and the second being given 3 days after the first infusion. The primary efficacy endpoint was the proportion of patients who achieved complete response (CR) of acute GVHD by study day 28. The study found that 66.7% (10/15) of patients treated with the high dose had a CR compared with 87.5% (14/16) of patients treated with the low dose. There were a number of secondary efficacy endpoints including, partial response (PR), time to best response, addition of escalated immunosuppressive therapy, and survival through to study day 90. Overall, the study showed that the low dose of Prochymal (2 x 10^6 MSCs/kg) appeared to be as effective as the higher dose (8 x 10^6 MSCs/kg) in inducing a response. The response criteria in this study were consistent with those in Protocol 280 (see Table 1).

Table 1: Acute GVHD response criteria definitions

Complete response (CR)	resolution of acute GVHD in all involved organs.
Partial response (PR)	decrease by at least 1 GVHD Grade in any 1 organ system without any worsening in any other organ system.
Overall response (OR)	defined as CR + PR
Durable response	a response lasting for at least 28 days (e.g., improvement in GVHD Grade).
Mixed response (MR	improvement by at least 1 stage in at least 1 evaluable organ with worsening by at least 1 stage in at least 1 other organ.
No response (NR):	stable or worsening disease: (1) stable - the absence of any clinically significant differences (improvement or worsening) sufficient to meet minimal criteria for improvement or deterioration in any evaluable organ; (2) worsening - deterioration in at least 1 organ system by 1 stage or more with no improvements in any other organs.
Flare	recurrence of acute GVHD after a CR.
Very Good Partial Response (VGPR)	an exploratory endpoint defined as: skin - residual erythematous rash <25% body surface area without bullae (residual faint erythema and hyperpigmentation did not count); liver - total bilirubin <2 mg/dL or <25% of the bilirubin level before the first treatment dose; gut - eating solid foods or tolerating enteral feed (adults only); predominantly formed stools; no overt GI bleeding or abdominal cramping; no more than occasional nausea and/or vomiting.

While Kebriaei et al (2009) was not designed to assess the optimal dose and schedule of Prochymal administration, 5/24 (20.8%) patients who achieved an initial CR had an acute GVHD flare requiring second-line therapy during the first 28 days following initiation of treatment. These GVHD flares suggested to the authors that 2 doses of Prochymal may be insufficient to maintain a CR. Furthermore, the authors noted that Le Blanc et al (2008) had found that multiple infusions were needed to achieve a sustained response in more that half of the patients treated with MSCs for steroid refractory GVHD. In view of the reported clinical experience in single-use protocols suggesting that more than 2 infusions would be required for patients with more severe forms of acute GVHD, Osiris specified that an initial treatment regimen of 8 infusions of 2 x 10^6 cells/kg over a 4 week period were to be used in Protocols 280 and 275.

> **Comment:** The submission included no formal dose finding studies. In Kebriaei et al (2009), an inverse relationship was observed between MSC dose and CR at 28 days with the lower dose (2 x 10^6 MSCs/kg) showing a greater response than higher dose (8 x 10^6 MSCs/kg).[1] However, the study was not designed to assess the optimal Prochymal dose and administration regimen.

[1] .CR rate was 10/15 (66.7%) for high dose and 14/16 (87.5%) for low dose.

7. Clinical efficacy

7.1. Acute GVHD – corticosteroid refractory disease

7.1.1. Pivotal study – Protocol 280

7.1.1.1. Study design, objective, locations, and dates

The pivotal study was titled – 'A Phase III, Randomized, Double Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Prochymal (Ex-vivo Cultured Adult Human Mesenchymal Stem Cells) Infusion for the Treatment of Patients Who Have Failed to Respond to Steroid Treatment for Acute GVHD (BB-IND No. 7939-Prochymal)'.

The **study was sponsored** by Osiris Therapeutics Inc and identified as Osiris Protocol Number 280. It was conducted in 72 study centres in 7 countries (United States, Canada, Australia, Germany, Italy, Spain, and the United Kingdom). The first patient was enrolled on 17 August 2006 and the last patient completed on 27 May 2009.

The **objectives of the study** were:

1. To evaluate the efficacy of Prochymal in patients with Grades B-D acute GVHD, who have failed to respond to steroid treatment.
2. To gather additional information on the safety of Prochymal in patients with Grades B-D acute GVHD, who have failed to respond to steroid treatment.

The study was conducted in accordance with Good Clinical Practice (GCP) as required by the International Conference on Harmonisation (ICH) guidelines and in accordance with country specific laws and regulations governing clinical studies of investigational products. Compliance with these requirements conforms with the ethical principles of the Declaration of Helsinki. The written study patient information, informed consent form, and other appropriate study related information were reviewed and approved by an Independent Ethics Committee (IEC) or Institutional Review Board (IRB) at each study site. Written informed consent was provided by all patients or, where appropriate, the patient's legal representative (e.g., paediatric patients).

7.1.1.2. Inclusion and exclusion criteria

The patient population consisted of males and females, between the ages of 6 months and 70 years (inclusive). Patients were required to have Grades B-D acute GVHD that had failed to respond to steroid treatment, and was secondary to allogeneic HSCT (bone marrow, peripheral blood stem cells, or cord blood cells) or DLI. The inclusion criteria defined failure to respond to steroid treatment as any Grade B-D (IBMTR grading) of acute GVHD that showed no improvement after 3 days and a duration of no greater than 2 weeks, while receiving treatment with methylprednisolone (≥1 mg/kg/day) or equivalent. The IBMTR severity index criteria for Grading (A-D) acute GVHD are summarised below in Tables 2 and 3.

Table 2: Organ staging of aGVHD (from IBMTR Index)

Organ	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
Skin	No rash	Rash < 25% BSA	Rash ≥ 25 to ≤ 50%	Rash > 50% generalized erythroderma	Plus bullae and desquamation
GIT	Diarrhoea < 500 mL/day	Diarrhoea 501 – 1000 mL/day	Diarrhoea 1001 – 1500 mL/day	Diarrhoea > 1500 mL/day	Severe abdominal pain ± ileus
Upper GIT	No protracted nausea/vomiting	Severe nausea/vomiting			
Liver	Bilirubin < 2 mg/dL	Bilirubin 2.1-3.0 mg/dL	Bilirubin 3.1-6.0 mg/dL	Bilirubin 6.1-15 mg/dL	Bilirubin > 15 mg/dL

Table 3: Grading index of aGVHD (from IBMTR Index)

	Grade A	Grade B	Grade C	Grade D
Skin	Stage 1	Stage 2	Stage 3	Stage 4
GIT	Stage 0	Stage 1-2	Stage 3	Stage 4
Upper GIT	Stage 0	Stage 1		
Liver	Stage 0	Stage 1-2	Stage 3	Stage 4

At study entry, adult patients were required to have a minimum Karnofsky Performance Status score of at least 30 (i.e., severely disabled; hospitalisation indicated; death not imminent), and paediatric patients were required to have a minimum Lansky Play Scale score of 30 (i.e., in bed; needs assistance even for quiet play).

In addition to the pre-specified inclusion and exclusion criteria, the protocol also included criteria for removal of patients from therapy or assessment. These included evidence of impaired respiratory function based on clinical assessment and/or deteriorating SaO2/saturation (SAT), and adverse events considered by the investigator to be related to the investigational agent.

> **Comment:** The IBMTR criteria used to grade the severity of acute GVHD are satisfactory. The inclusion criteria included patients who were refractory to corticosteroid steroids (consistent with the proposed indication), but refractoriness to other immunosuppressive agents was not an inclusion criteria (inconsistent with the proposed indication). In fact, patients were excluded if they had received primary treatment for acute GVHD with agents other than corticosteroids.

7.1.1.3. Study treatments

Investigational agent (Prochymal or placebo)

In this study, patients were randomized 2:1 to Prochymal or placebo (double-blind). Patients were evaluated for efficacy and safety until death, withdrawal or 180 days post first infusion (Study Day 0), whichever occurred first.

Prochymal was formulated in a cryogenic bag to a total volume of 15 mL in Baxter Plasma-Lyte A, 50 g/L HSA, and 100 mL/L DMSO. Each bag contained approximately 100 x 10^6 hMSCs, and each Prochymal dose was held at liquid nitrogen vapor phase temperature (less than or equal to -135°C) until thawed and reconstituted immediately prior to administration.

Placebo was formulated in a cryogenic bag to a total volume of 15 mL of Baxter Plasma-Lyte A, 50 g/L HSA and 100 mL/L DMSO. Each placebo dose was held under the same conditions as Prochymal until thawed and was reconstituted immediately prior to administration.

Administered treatments

The Investigational Agent was administered iv at a controlled rate of 4-6 mL/minute via infusion pump for patients weighing ≥ 35 kg, and for patients weighing < 35 kg the Investigational Agent was infused over 60 minutes. No other medications were given during the infusion unless determined to be medically necessary by the Investigator.

Initial treatment

Initial treatment consisted of the Investigational Agent twice per week for 4 consecutive weeks. Pre-medication, consisting of hydrocortisone and diphenhydramine was administered at least 30 minutes prior to the infusion of the Investigational Agent: i.e., 25-50 mg iv of both hydrocortisone and diphenhydramine for adult patients; and 0.5-1 mg/kg (up to 50 mg) iv of both hydrocortisone and diphenhydramine for paediatric patients.

Patients randomised to Prochymal received iv infusions at a dose of 2 x 10^6 hMSC/kg (actual body weight), and patients randomised to placebo received iv infusions equivalent to the calculated volume they would have received with the active treatment. All patients were to receive all 8 infusions as initial treatment by Study Day 28. Infusions were administered at least 3 days apart.

Continued treatment

On Study Day 32 (± 2 days), patients were assessed in order to determine whether continued study treatment was indicated. If a patient had a Complete Response (CR), no additional Investigational Agent was administered. If a patient had No Response (NR), no additional Investigational Agent was administered. If a patient had a Partial Response (PR) or a Mixed Response (MR), additional infusions of the Investigational Agent were administered once per week for an additional 4 weeks according to original randomisation. The Investigational Agents were administered in combination with GVHD therapies in accordance with institutional guidelines in both the initial and continued treatment periods.

Treatment for GVHD flare

Patients who experienced a significant GVHD flare (Grades B-D) after achieving a CR and prior to Study Day 72 had the option to be retreated with Investigational Agent infusions as per the initial treatment plan. Additional GVHD therapies were administered as per institutional guidelines. Patients who had achieved a CR and who had a subsequent flare of acute GVHD could have an increment to corticosteroid dosing or PUVA (Psoralen + long wave ultraviolet radiation) therapy. Patients continued to be followed according to the Schedule of Study Assessments and were assessed on each study day of infusion. Study days did not restart at the time of treatment for flare, but were continued to be counted from the first infusion for original steroid-refractory acute GVHD. Patients were only treated for GVHD flare once and were not treated with Prochymal after Study Day 100.

Prior and concomitant treatments

In both the Prochymal and placebo treatment groups, patients received open-label institutionally defined standard of care for acute GVHD (e.g., maintenance of corticosteroid steroid treatment and the addition of a second-line therapy) in addition to the randomised, double-blind Investigational Agent. It should be noted that each Investigator continued to treat with corticosteroids according to institutional guidelines. In addition to the randomised Investigational Agent plus corticosteroids and second-line therapies, all patients may have received transfusion support per institutional practice, and anti-infective prophylaxis directed towards CMV, gram positive (encapsulated) bacteria, Pneumocystis carinii, and fungal infections per institutional practice.

If improvement in GVHD was observed for a period of 3-5 days, then it was recommended that methylprednisolone or equivalent be tapered in accordance with institutional guidelines. The target was to have discontinued steroids 10 weeks after initiating the taper.

Protocol guidelines for escalating therapy of acute GVHD included worsening of symptoms for at least 3 days, unimproving Grades C-D GVHD persisting for at least 1 week despite treatment, and unimproving Grade B GVHD persisting for at least 2 weeks despite treatment.

Concomitant medications that had not been approved for any indication by the FDA were not given within 30 days prior to randomisation, or during the study from the time of the first infusion to the end-of-study visit.

7.1.1.4. Study assessments

Assessment of acute GVHD

The severity of acute GVHD was assessed by a physician using IBMTR Grading (see Tables 2 and 3). At each study site, the presence or absence of acute GVHD grade B-D of the skin, liver, and

gut were determined for each participating patient. Acute GVHD assessments were performed weekly on all patients beginning at screening/baseline through Day 99, and on Days 32, 100, 130, 160, and 180/End-of-study. The collected information included the percentage of skin rash involvement, volume of stool output, and level of weekly maximum reported bilirubin level. All efficacy response analyses were based on GVHD grades and organ staging from the GVHD Assessment Case Report Form (CRF) at Screening/Baseline. Documentation of biopsy confirmation of target organs was recommended in the Protocol, but was not mandatory.

Response criteria

All efficacy response analyses were based on GVHD grades and organ staging from the GVHD Assessment CRF at Screening/Baseline. The definitions of the response criteria are summarised in Table 1.

7.1.1.5. Efficacy variables and outcomes

Primary efficacy variable

The primary efficacy endpoint was complete response (CR) of ≥ 28 days duration (i.e., durable CR) within 100 days post first infusion in the intent-to-treat (ITT) population.

Additional efficacy variables (endpoints)

The secondary efficacy endpoints analysed in the modified intent-to-treat population (mITT) population were:

- Survival at 100 (±3 days) days post first infusion
- Survival at 180 days (±7 days) post first infusion
- Cumulative steroid usage.

Additional efficacy variables 'of interest' analysed in the mITT population were:

- Incidence of Overall Response (CR + PR) by organ at days 28 and 100
- Time to CR
- Durability of organ response
- Change from baseline in quality of life (QoL) and Karnofsky/Lansky Performance Status assessments and
- Additional exploratory analyses outlined in the statistical analysis plan (SAP) including induction, duration and time to different definitions of response (e.g., VGPR; induction of two grade reduction).

Subgroup analyses

The SAP specified a number of analyses of the primary and secondary efficacy variables by subgroups including: GVHD grade at study entry (B, C, D); age group (<18 years; ≥ 18 years); gender (male, female); and donor compatibility (related, unrelated). There were also a number of other subgroup analyses specified in the SAP (eg. subjects who escalated past second line therapy; subgroup analysis of second line therapy; time on steroids before randomisation [3-14 days vs > 14 days]; subjects with upper or lower GIT involvement).

> **Comment:** The primary and secondary efficacy endpoints chosen for this study are considered to be appropriate and clinically meaningful. The primary endpoint stresses the importance of the durability of the CR (i.e., maintained > 28 days), while the two secondary survival endpoints at days 100 and 180 underline the clinical importance of these objectively determined outcomes for a serious life-threatening condition. Information in the Clinical Overview (Module 2.5) indicates that the efficacy endpoints were decided following discussion between Osiris and the FDA.

The are no TGA adopted European Union guidelines relating to the assessment of medicines for the treatment of acute GVHD. However, in the Clinical Summary of Efficacy (Module 2.7.3) Osiris states that that '[R]eduction in aGVHD symptoms, as captured by grading schemes, corresponds to an immediate improvement in quality of life. Combined with evidence that achieving a response correlates with improved chances of survival, reaching a timely OR (e.g., 28 days after initiation of treatment) is the appropriate endpoint for consideration of efficacy in the treatment of aGvHD' (Section 2.7.3.1.1.6). Osiris supports its argument that the OR (particularly at 28 days) is the appropriate efficacy endpoint by reference to - (1) the outcomes of a 'Workshop on Clinical Trials Endpoints for Acute GvHD after Allogeneic HSCT' held in the USA in May 2009 to seek consensus on clinically significant endpoints for evaluating potential treatments for aGvHD; (2) advice obtained from clinical experts; and (3) published data from MacMillan et al (2010).

The 'workshop' (2009) was co-sponsored by the National Heart, Lung, and Blood Institute (NHLBI), the FDA, the CIBMTR, the American Society for Blood and Marrow Transplantation (ASBMT) and the National Institute of Allergy and Infectious Disease (NIAID). Osiris stated that during the 'workshop', the 'subject matter experts agreed that overall response (OR), defined as complete response (CR) + partial response (PR) at Day 28, is a clinically meaningful endpoint that correlates with survival (MacMillan, 2010; Weisdorf, 2009)'. The slides from the 'workshop' summarising the presentations are available on the CIBMTR website (CIBMTR, GVHD Workshop, 2009). Perusal of these slides suggests that CR/PR were considered to be clinically meaningful responses, and that CR/PR (Day 28 and Day 56) and survival were considered to be reasonable endpoints for regulatory purposes.

The Macmillan et al 2010 publication referred to by Osiris has also been examined. In this publication, the authors state that the optimal primary and early endpoint from prospective GVHD therapeutic clinical trials has not been established. Consequently, in order to investigate potentially clinically meaningful endpoints they undertook a retrospective analysis of 864 patients with acute GVHD who received initial therapy with prednisone 60 mg/m2/day for 14 days followed by an 8 week taper. In a multiple regression analysis, patients with no response at day 28 were 2.78 ([95% CI: 2.17-3.56], $p<0.001$) times more likely to experience transplant-related mortality (TRM) prior to 2 years than patients with a response. The authors concluded that 'these data suggest that day 28 is the best early endpoint for acute GVHD therapeutic trials in predicting 2 year TRM'. The author's also found that CR or PR at days 28 and 56 were each valuable as early measures of favourable improvement and predicted 2 year TRM, and that the 28 and 56 day data were superior to the 14 day data. Factors identified in the study as being associated with significantly worse 2 year TRM included: older age; high risk disease; severe GVHD; and partially matched related bone marrow (BM)/peripheral blood (PB) donor source.

Osiris, in discussing the efficacy outcomes from Protocol 280, appeared to focus primarily on the importance of the OR at Day 28 while downplaying the relevance of the results from the pre-specified primary and secondary efficacy endpoints. In particular, Osiris appeared to minimise the importance of the Day 100 and 180 survival data by stating that '[o]nce past the treatment phase and especially beyond Day 100, there are many competing risks for this severely ill patient population with a life-threatening disease, which cannot be controlled within the framework of a clinical trial. These confounding factors make it difficult to evaluate survival at later times' (Module 5, Protocol 280, Section 11.4.4). However, in this CER, evaluation of efficacy for the purposes of recommending acceptance or rejection of

the application to register Prochymal has concentrated primarily on the pre-specified primary and secondary efficacy outcomes from Protocol 280. While the additional endpoints (including OR survival at Day 28) are of interest, it is considered that in Protocol 280 these endpoints were primarily exploratory and hypothesis generating. Further comment on Osiris' approach to the interpretation of the efficacy outcomes from Protocol 280 will be provided later in this CER (see Section 7.1.5).

7.1.1.6. Randomisation and blinding methods

All patients who signed an informed consent form and met all of the inclusion and none of the exclusion criteria were randomised in a blinded fashion using a central Interactive Voice Response System (IVRS) on a 2:1 basis to either the Prochymal or the placebo control group. Patients were stratified and balanced by grades of GVHD (B and C/D).

The study was double-blinded. The treatment each patient received was not disclosed to the Investigator, study site personnel, patient, sponsor, or the contracted clinical research organisation (except for the unblinded analysis team servicing the data safety monitoring board [DSMB] and the unblinded monitor). Only designated technicians in the Central Processing Laboratory at the study sites were unblinded to treatment, and designated cell processing technicians prepared both the Prochymal and placebo infusions. The Prochymal and placebo infusions were prepared in identical infusion bags and infused with similarly masked infusion tubing. The designated technician in the Central Processing Laboratory was responsible for maintaining the Investigational Agent records including randomised treatment assignments by patient identification. The blinded treatment information was to be broken only in an emergency when knowledge of such treatment could have an impact on a further treatment decision or aid in the emergency treatment of the patient.

The database lock occurred following assignment of all disposition codes, finalisation of the statistical analysis plan, signing off of outstanding queries, database audit completion, and resolution of issues raised during the blinded review of data. Complete study unblinding occurred following database lock and signed authorisation from the sponsor.

7.1.1.7. Analysis populations

The intent-to-treat (ITT) population included all patients who had been randomised. Both the modified intent-to-treat (mITT) population and the safety population included all patients who had been randomised and received at least 1 dose of Investigational Agent. The per-protocol (PP) population included mITT patients who were compliant to the treatment plan and adherent to key inclusion/exclusion criteria.

The primary efficacy analysis was based on the ITT population. Additional efficacy analyses of the efficacy endpoints identified as secondary and exploratory analyses in the SAP were based on the mITT population as well as the per protocol (PP) population. Safety analyses were based on the safety population.

7.1.1.8. Sample size

A total of 240 male and female patients aged 6 months to 70 years, inclusive, were planned to be randomised and treated in a ratio of 2:1 Prochymal to placebo. Assuming a 49% primary efficacy response rate (CR of ≥ 28 duration) for the Prochymal treated patients (an improvement of 20% over historical controls), and a response rate of 29% for the placebo treated patients, 160 active treatment patients and 80 placebo provided a power of 80% with alpha=0.05.

> **Comment:** The ITT population included 260 patients (173 in the Prochymal group and 87 in placebo group). Based on these figures, and the assumptions used to calculate the sample size, it can be concluded that the study was adequately powered to analyse the primary efficacy endpoint.

7.1.1.9. Statistical methods

Primary analysis

The primary efficacy analysis was the comparison of the clinical success rate of Prochymal versus placebo in achieving a CR sustained for ≥ 28 days in the ITT population. During the interval of sustained response, the duration of CR was the first CR date recorded to the date of first flare after the CR or to the date of the last CR if there was no flare, inclusive of both dates. In addition to the primary analysis in the ITT population, analyses were also undertaken in the mITT and PP populations.

For the primary analysis, the Cochran-Mantel-Haenszel (CMH) test stratified by GVHD Grade at steroid refractory diagnosis (B versus C/D) was used to compare the two treatment groups. The null hypothesis tested was that there was no significant difference in the success rate between the treatment groups, while the alternate hypothesis tests that there was a difference between the two treatment groups. The CMH test stratified by the unique GVHD Grade at steroid refractory diagnosis (B versus C versus D) was also performed (exploratory analysis).

> **Comment:** The primary analytical methods are considered to be satisfactory. The submission included the original SAP dated 6 July 2009. The SAP was comprehensive and included detailed summaries of the statistical methods employed in the study. Examination of the SAP showed that standard and appropriate analytical methods were employed to investigate the data. The SAP included provision for interim analyses by an independent Data Safety Monitoring Board (DSMB) based on unblinded data and possible early termination of the study due to safety concerns or overwhelming efficacy. Two interim analyses were planned when 50% and 75% of randomised subjects had completed treatment. However, while planned, no interim analyses were undertaken. At the time of the first safety review planned for when 50% of randomised subjects had completed treatment actual enrolment was 75% complete, and the sponsor decided not to spend any alpha by undertaking an interim analysis. The DSMB agreed to the procedural changes. The submission also included documentation relating to 'Changes to planned statistical analysis' dated 19 January 2010 (i.e., after unblinding but before completion of the final statistical study report). The changes have been examined and are considered not to have compromised the validity of the final statistical analysis. The changes mainly related to clarification of ambiguities in the original SAP concerning recording of endpoints.

Secondary analyses and additional analyses

The secondary analyses were the analyses of the three secondary efficacy endpoints. Examination of the methods used to analyse these endpoints are comprehensively documented in the SAP. The CMH test stratified by GVHD Grades at steroid refractory diagnosis (B versus C/D) was used to compare survival status of the two treatment groups for patients in the mITT. This analysis was repeated, stratifying by unique GVHD Grades at steroid refractory diagnosis (B versus C versus D) for patients in the mITT population (exploratory analysis). Cumulative steroid usage was based on the steroid therapies recorded post-infusion. The average daily dose of steroid equivalent to methylprednisolone on Days 7, 14, 21, 28, 35, 42, 49, and 56 was summarised by treatment group. Daily dose for each patient was calculated based on the unit dose and the frequency of the dose for the specified day. Only methylprednisolone and prednisolone were included. The statistical methods used to analyse the additional efficacy endpoints have been examined are considered to be satisfactory.

General statistical methods

Categorical variables were summarised using frequencies and percentages, and continuous variables were summarised using standard descriptive statistics. All confidence intervals (CIs) had a 95% confidence level. Statistical tests and resulting p-values were reported as two-sided

and were assessed at the overall significance level of 5% unless otherwise specified. However, no adjustments of significance levels were undertaken for multiplicity of testing.

In general, the baseline value for a variable was defined as the last non-missing observation prior to or equal to the first dose date of Investigational Agent. Data collected at unscheduled time points were not summarised at the unscheduled time points. However, the unscheduled data were considered when summarising the last observed value. Study Day was calculated as the assessment date minus first infusion date.

Missing data

The GVHD assessment should have been staged completely for all organs, and a missing organ stage was not imputed. A missing weekly assessment at a post-baseline visit up to Study Day 100 was imputed based on the worst grade the week immediately prior to the missing assessment or the week immediately following the missing assessment. If the grade from the previous week prior to the missing assessment and the grade of the week following the missing assessment did not match, the worse of the 2 grades were used for imputation. If more than 1 consecutive weekly assessment was missing, the grades for those visits were not imputed.

For the determination of Survival at 100 days (±3 days) and 180 (±7 days) days post first infusion, if the patient's status was unknown or the patient was lost to follow-up then those patients were considered not alive at Day 100 or Day 180 in the survival summaries. For the QoL assessments, missing item scores were imputed based on the average of the non missing scores for FACT-G-BMT and for the SF-36. No other imputations were performed.

7.1.1.10. Participant flow

Of the 260 enrolled patients, all 260 (100%) were randomised to study treatment (173 [66.5%] to Prochymal; 87 [33.5%] to placebo). In total 223 patients (85.8%) completed the study and 37 patients (14.2%) discontinued prematurely. Of the 37 patients who discontinued prematurely, 5 discontinued due to an AE, 11 withdrew consent, 1 was lost to follow-up, and 20 were included in the category of 'Other' (e.g., patient too ill to continue; Investigator made a decision not to continue to treat the patient; or the patient was one of the 16 randomised untreated patients).

7.1.1.11. Major protocol violations/deviations

There were 38 patients with major and/or minor protocol deviations who did not meet at least 1 or more of the inclusion criteria (n=25), or the exclusion criteria (n=16). Of these 38 patients, 6 were excluded from randomisation due to the seriousness of the protocol deviation. Examination of the listed protocol deviations indicates that the majority were relatively minor and randomisation of these patients is considered unlikely to have biased the study. There were 43 patients with treatment plan violations, including the number of investigational agent infusions, the rules for continuation therapy, the number of second line agents, and the requirement to administer Prochymal and second line agents within a 4 day window.

7.1.1.12. Baseline data

In the overall ITT population (n=260), the mean±SD age of patients was 42.3±17.2 years, and the majority of patients were aged ≥ 18 years (89.2%) with the minority being aged < 18 years (10.8%). The majority of patients in the overall ITT population were categorised as 'white (83.5%). In the ITT population, baseline demographic characteristics were generally well balanced between the Prochymal and placebo groups. However, the proportion of patients aged < 18 years in the ITT population was notably greater in the placebo group (16.1%) than in the Prochymal group (8.1%), but the number of patients aged < 18 years was small in both groups (14 in each group).

There were no significant imbalances between the Prochymal and placebo groups as regards the underlying malignancy or leukemic disease at transplant, with the most frequent individual condition in both groups being acute myeloid leukemia - primary (28.3% and 26.4%,

respectively). The 'other' category of underlying malignancy or leukemic disease at transplant was the most commonly occurring category in both the Prochymal (37.6%) and placebo (35.6%) groups, and numerous haematological conditions were included in this category.

The most common conditioning regimen was myeloablative: 65.3% of the Prochymal group and 73.6% of the placebo group. GVHD prophylaxis was comparable between the groups, and unrelated donor compatibility was 57.8% for the Prochymal group and 59.8% for the placebo group. Transplant type was similar in the two treatment groups, with the predominant transplant type being PBSC in both the Prochymal (78.0%) and placebo (71.3%) groups.

There was a notable imbalance between the two treatment groups in the proportion of patients with steroid refractory Grade D acute GVHD (27.2% for Prochymal, 16.1% for placebo). Steroid refractory Grades B and C were more evenly balanced between the two treatment groups: Grade B (22.0% vs 26.4%, Prochymal and placebo, respectively); Grade C (50.9% vs 57.5%, Prochymal and placebo, respectively). The duration and extent of steroid refractory disease, as measured by days on steroid prior to randomisation, was greater than 14 days for 37.0% of patients of in the Prochymal group and 33.3% of patients in the placebo group. Organ staging was similar for the two treatment groups. However, the proportion of patients with two organ involvement was greater in the placebo group (46.0%) than in the Prochymal group (32.9%), and where two organs were involved the skin + gut combination occurred more frequently than the other two possible combinations.

Second line therapies differed between the two treatment groups. Though 28 patients (23 [13/3%] Prochymal; 5 [5.7%] Placebo) had second line therapy categorised as 'None', all patients had received a second line therapy while on study. The patients recorded as 'None' (i.e., not receiving second line therapy) included randomised untreated patients, patients who began second line therapy outside of the designated window of Day -4 to Day +7 (relative to first dose date), or patients whose second line therapy was recorded incorrectly on the GVHD Therapy Dose CRF page as a prior medication or a third or fourth line therapy.

The baseline medical history of the ITT population has been examined and showed no notable differences between the two treatment groups. Baseline concomitant medications in the safety population have been examined and there were no notable differences between the two treatment groups. Overall, the 10 most commonly used concomitant medications were: aciclovir (62.7%); lorazepam (62.7%); paracetamol (60.2%); furosemide (54.1%); pantoprazole (52.5%); vancomycin (50.4%); voriconazole (45.5%); ursodeoxycholic acid (44.3%); bactrim (43.9%); and tacrolimus (41.8%). At baseline, all patients were on corticosteroid therapies. Overall, the most commonly used corticosteroids in ≥ 10% of patients in the safety population at baseline were: methylprednisolone (57.8%); prednisone (40.2%); methyl prednisolone sodium succinate (30.3%); and budesonide (15.2%). Overall, the most commonly used GVHD therapies in ≥ 10% of patients in the safety population at baseline were: mycophenolate mofetil (32.0%); infliximab (21.7%); tacrolimus (20.9%); antithymocyte globulin (16.8%); etanercept (12.7%); daclizumab (12.3%); and ciclosporin (11.9%). Overall, the most commonly GVHD prophylaxis therapies in ≥ 10% of patients in the safety population were: tacrolimus (51.2%); ciclosporin (47.5%); mycophenolate mofetil (36.5%); and methotrexate (34.4%).

7.1.1.13. Results for the primary efficacy variable

The primary efficacy endpoint of CR ≥ 28 days duration within 100 days post first infusion for both treatments in the ITT population is summarised below in Table 4.

Table 4: Protocol 280 – Complete response of ≥ 28 days duration by treatment group (PCL = Prochymal; PBO = placebo) and GVHD grade; ITT population

	GVHD Overall (Grade B/C/D)			GVHD Grade B		GVHD Grade C/D	
	PCL (n=173)	PBO (n=87)	p-value	PCL (n=38)	PBO (n=23)	PCL (n=135)	PBO (n=64)
Responder	34.7% (n=60)	29.9% (n=26)	p = 0.423	39.5% (n=15)	30.4% (n=7)	33.3% (n=45)	29.7% (n=19)
Non-Responder	65.3% (n=113)	70.1% (n=61)		60.5% (n=23)	69.6% (n=16)	66.7% (n=90)	70.3% (n=45)

Note: Responder is defined as a subject with a complete response of 28 days or more. Non-responder includes subjects who have no recorded CR, or a CR lasting less than 28 days.
Note: P-value is from the Cochran-Mantel-Haenszel (CMH) test stratified by GVHD grade at diagnosis/study entry.
Note: Data for this analysis is based on GVHD assessments recorded on the CRF up to Day 100.

Comment: There were no statistically significant differences in the complete response rate of ≥ 28 days between the Prochymal and placebo GVHD (Grade B/C/D) groups in the ITT population. The results of analysis in the mITT were similar to those for the analysis in the ITT population. The results of the PP analysis of the CR ≥ 28 days in the GVHD (Grade B/C/D) groups showed a greater absolute difference between Prochymal and placebo than in the corresponding ITT analysis (11.2% and 4.8%, respectively), but the difference between the two treatment groups in the PP population was not statistically significant (p=0.087). In the ITT population, the results by unique Grade showed that response rates for Grade B and Grade C were comparable, and response rates for Grade D were the lowest, as expected for the most severe GVHD. There was no statistically significant difference between the two treatment groups when the GVHD population was analysed by unique Grade (p=0.310; CMH test stratified by grade at diagnosis). In the Kaplan-Meier analysis, median time to complete response was 21 days [95% CI: 16, 28] in the Prochymal groups and 25 days [95% CI: 17, 32] in the placebo group; p=0.262, stratified Wilcoxon Rank Sum test.

7.1.1.14. Results for other efficacy endpoints

Secondary efficacy endpoints

Survival at 100 (±3 days) days post first infusion (mITT population)

There was no statistically significant difference between the Prochymal and placebo groups in the proportion of patients in the mITT population surviving for greater than 100 days post first infusion (52.1% [85/163] vs 50.6% [41/81], respectively; p=0.780, CMH stratified by GVHD at diagnosis/study entry).

Survival at 180 days (±7 days) post first infusion (mITT population)

There was no statistically significant difference between the Prochymal and placebo groups in the proportion of patients in the mITT population surviving for greater than 180 days post first infusion (34.4% [56/163] vs 42.0% [34/81], respectively; p=0.274, CMH stratified by GVHD at diagnosis/study entry). The median survival time in both treatment groups was 115 days, and there was no statistically significant difference between groups in overall survival time (p=0.519, log-rank test).

Cumulative steroid usage

The average daily steroid use through to Day 56 computed at weekly intervals was summarised. The results were presented descriptively and no analyses were undertaken for the pairwise comparisons. Overall, there were no marked differences between the two treatment groups, and steroid use was generally similar or marginally lower in the placebo group compared with the Prochymal group.

Additional endpoints

In summarising the efficacy data, Osiris focused primarily on the additional endpoints which it claimed demonstrated clinical benefit of Prochymal compared with placebo (although these endpoints were generally not statistically significant), not the non statistically significant results for the protocol specified primary and secondary efficacy endpoints. In particular, Osiris appeared to emphasise the clinical importance of OR at Day 28. However, the difference between the two treatment groups in the OR at Day 28 (± 4 days) in the mITT population was not statistically significant: 57.7% (94/163) and 50.6% (41/81), Prochymal and placebo, respectively; p=0.224, CMH stratified by GVHD at diagnosis/study entry.

7.1.1.15. Paediatric subgroup analysis

Patient population

The submission included a separate statistical analysis of the paediatric subpopulation enrolled in Protocol 280 dated 26 May 2010. The paediatric subpopulation consisted of both male and female patients, aged between 6 months and < 18 years, with steroid refractory acute GVHD (Grade B/C/D) secondary to allogeneic HSCT (bone marrow, peripheral blood stem cells, or cord blood cells) or DLI.

Overall, 28 paediatric patients were enrolled and randomised (14 in each treatment group), and 25 (89.3%) completed the study (13 in the Prochymal group and 12 in the placebo group). Three patients (10.7%) discontinued; 1 Prochymal patient and 1 placebo patient withdrew for reasons categorised as 'Other', and 1 placebo patient withdrew consent after receiving 3 infusions. Patients who died were considered to have completed the study, and a total of 10 patients (35.7%) died during the study (5 in each treatment group). An additional placebo-treated patient who died on Day 185 from a SAE that started on Day 172 was not counted as a death in the disposition and efficacy analyses.

In patients randomised to Prochymal (n=14), the mean±SD age was 6.5 ± 3.8 years (50.0% male, and 71.4% White), and in patients randomised to placebo (n=14), the mean±SD age was 9.3±5.7 years (71.4% males, and 64.3%, White). The mean height and weight were lower in the Prochymal group than in the placebo group, which reflects the mean age difference of about 3 years between the two treatment groups. Baseline disease characteristics of the two treatment groups were generally well balanced.

Efficacy endpoints and results

The following six pre-specified efficacy endpoints in Protocol 280 SAP were assessed in the paediatric subgroup (CR ≥ 28 days duration; survival at day 100; survival at Day 180; induction of complete response, OR at Day 28; and OR through Day 100). All efficacy endpoints were analysed in the ITT population (14 patients in each of the Prochymal and placebo groups) using the CMH test stratified by acute GVHD (i.e., the analyses in the paediatric subgroup were consistent with those in the total patient group). The study report also included separate results for the acute GVHD Grade B (n=6) and Grade C/D (n=22) groups. However, in this CER only the results from the overall acute GVHD B/C/D group (n=28) are presented (Table 5).

Table 5: Protocol 280 – Efficacy results in the paediatric subgroup (Grade B/C/D); ITT population

Efficacy Endpoint	Prochymal (n=14)	Placebo (n=14)	Effect size (Pro – Pbo)	p-value
CR ≥ 28 days duration	64.3% (9/14)	42.9% (6/14)	21.4%	p=0.274.
Survival at 100 days	78.6% (11/14)	50.0% (7/14)	28.6%	p=0.129
Survival at 180 days	64.3% (9/14)	50.0% (7/14)	14.2%	p=0.461.
CR through Day 100	71.4% (10/14)	50.0% (7/14)	21.4%	p=0.261
OR at Day 28	64.3% (9/14)	35.7% (5/14)	28.6%	p=0.139
OR through Day 100	85.7% (12/14)	57.1% (8/14)	21.4%	p=0.107

Note: p-value calculated by CMH test stratified by acute GVHD at study entry.

> **Comment:** The six efficacy endpoints all numerically favoured Prochymal over placebo in the paediatric subgroup, but none of the reported differences between the two treatment groups were statistically significant. The acute GVHD (Grade B/C/D) patient numbers in the two treatment groups are small. Consequently, the results should be interpreted with caution.

7.1.2. Other efficacy studies - supportive study protocol 275

7.1.2.1. Study design, objectives, location, and dates

The supportive study (identified as pivotal in the submission documents) was titled – 'Expanded Access of Prochymal (Ex-vivo Cultured Adult Human Mesenchymal Stem Cells) Infusion for the Treatment of Pediatric Patients Who Have Failed to Respond to Steroid Treatment for Acute GvHD'.

The study was sponsored by Osiris Therapeutics Inc. It enrolled paediatric patients from 31 study sites in 6 countries (United States, Canada, United Kingdom, Italy, Finland, and New Zealand). It was initiated on 18 August 2007, and all 59 patients who were enrolled from this date and had completed participation by 30 December 2009 were included in the interim report. The study report was dated 4 June 2010.

The objective of Protocol 275 was to allow paediatric patients who failed to respond to steroid treatment for acute GvHD to be treated with Prochymal. The study analysis was designed to: (1) evaluate the efficacy of Prochymal when used as a rescue agent in paediatric patients with acute GvHD (Grade B-D); and (2) document the safety profile and tolerability of Prochymal for the population for the given dosing regimen.

The phase of development was defined as 'treatment protocol'. The design of Protocol 275 was a single-arm, multi-centre study of paediatric patients aged between 2 months and 17 years (inclusive) with Grades B-D acute GvHD secondary to allogeneic HSCT or DLI who failed to respond to steroid treatment and other therapies. Failure to respond to steroid treatment was defined as acute GvHD Grade B-D that was not improving after at least 3 days of systemic steroid therapy (≥1 mg/kg/day methylprednisolone or equivalent). Patients were evaluated for safety until death, withdrawal, or 100 days post first infusion (Day 0), whichever occurred first. Survival status was also captured through 180 days post onset of acute GvHD to allow for comparison with external data.

The study was carried out in compliance with the protocol and in accordance with Osiris and Quintiles standard operating procedures. The study was designed to ensure adherence to Good Clinical Practice (GCP), the ethical principles of which have their origin in the Declaration of Helsinki, Title 21 of the Code of Federal Regulations Parts 50, 56, and 312, and the International Conference on Harmonisation (ICH) guideline E6 (R1) (Good Clinical Practice: Consolidated Guideline). The protocol and all relevant additional documents were reviewed and approved by relevant Institutional Review Boards (IRBs) or Ethics Committees (ECs) at each study site. Since all patients were under the age of 18, parenteral signature of informed consent was required.

> **Comment:** The major limitation of this Prochymal single-arm study was the absence of a placebo-control group. Osiris stated that the use of a placebo control 'was not considered [to be an option] for ethical reasons. Instead, a historical control was employed for the comparison of survival'. In Protocol 280, the sponsor justified the placebo control group because both active and placebo treatment groups also received the institutionally defined standard of care (e.g., a second-line therapy in addition to continued steroid treatment). However, Protocol 275 also permitted concomitant therapy and standard and supportive GVHD therapy administered at the Investigator's discretion in accordance with site-specific institutional policies. Therefore, it appears to be inconsistent to state that a placebo control was not considered to be an option for

'ethical reasons' in Protocol 275, but was permitted in Protocol 280 and approved by IECs/IRBs at 72 sites in the 7 countries in which the study was undertaken (i.e., USA, Canada, Australia, Germany, Italy, Spain, and the UK).[2] It appears from the discussion in the Clinical Overview (Module 2.5) that Protocol 275 was designed as an open-label study without a placebo control for those paediatric patients for whom their treating physicians specifically wanted to treat with Prochymal rather than enrol them in Protocol 280.

7.1.2.2. Inclusion and exclusion criteria

The inclusion criteria were:

- Parental signature of informed consent
- Patients (male and female) 2 months to 17 years of age, inclusive
- Patients had failed to respond to steroid treatment for Grades B-D acute GVHD: failure to respond to steroid treatment for acute GVHD was defined as any Grades B-D acute GVHD that was not improving after at least 3 days of methylprednisolone ($\geq$ 1 mg/kg/day) or equivalent
- Patients must not have had a known allergy to bovine or porcine products
- Patients must not have received a transplant for a solid tumor disease and
- Patients must not have had evidence of a pulmonary infiltrate or diffuse alveolar haemorrhage and must have been unlikely to require more than 2 L of oxygen via face mask or an estimated FiO2 of 28% via other delivery methods in order to sustain an O2 saturation of 92% during the next 3 days.

There were no exclusion criteria. The study included standard criteria for removal of patients from the study and for follow-up of patients who had discontinued. Patients who died were considered to have completed the study.

7.1.2.3. Study treatments

All patients received iv infusions of Prochymal at a dose of 2 x 10^6 hMSC/kg (actual body weight) twice per week for 4 consecutive weeks, for a total of 8 infusions by Day 28. Infusions were to have been administered at least 3 days apart.

Response to initial therapy was assessed on Day 28 (±2 days) in order to determine whether continued treatment was indicated. If eligible, patients were given iv infusions of Prochymal (at a dose of 2 x 10^6 hMSC/kg body weight) once per week for an additional 4 weeks.

Eligibility for continued treatment was determined as follows:

- if a complete response (CR) was observed, then no additional Prochymal infusions were administered
- if no response (NR) was observed, then no additional Prochymal infusions were administered
- if a partial Response (PR) was observed and no safety issues were attributed to Prochymal, patients were eligible to receive continued therapy

[2] Sponsor comment: 'The patients in Protocol 275 were very severely ill, even more so than in Protocol 280. GvHD is a life threatening disease in all cases, but the Protocol 275 patients had failed two agents for GvHD treatment in addition to steroids. Therefore, randomisation of these patients to a placebo arm was not feasible and the sponsor stated that this would have been unethical.'

- if a mixed response (MR) was observed and no safety issues were attributed to Prochymal, patients were eligible to receive continued therapy.

The definitions of the response criteria were the same as those in Protocol 280.

Patients may have received treatment up to Day 100. Patients were assessed for GVHD status and for safety until death, withdrawal, or 100 days post first infusion, whichever occurred first.

Patients who had a GVHD flare after achieving a CR and before Day 72 were treated with Prochymal infusions per the initial 28 treatment plan described above (i.e., 2 infusions twice weekly for 4 weeks). Patients were treated for GVHD flare once only, and were not to have been treated with Prochymal after Day 100.

Patients whose GVHD had responded to therapy, but who had not achieved a CR after the first 8 weeks, could have received an additional 4 weeks of 2 x 10^6 hMSC/kg of Prochymal administered once per week.

Prochymal treatments were administered in combination with GVHD therapies in accordance with institutional guidelines. During the treatment with Prochymal, the standard of care for GVHD was administered to patients at the discretion of the Investigator. Prochymal was formulated and supplied in the same manner as Protocol 280.

7.1.2.4. Study assessments

Acute GVHD assessments were performed at screening (Day -3 to Day -1), Day 28 (±2), and Day 100 (±7 days)/End-of-treatment. The severity of acute GvHD was assessed using International Bone Marrow Transplant Registry (IBMTR) Grading (as for Protocol 280), Patients were evaluated for the presence or absence of acute GVHD of the skin, liver, and gut. Clinical assessments were to have been made consistently by an Investigator.

7.1.2.5. Efficacy variables and outcomes

Primary endpoint

The primary endpoint was the overall response rate (CR or PR) to Prochymal at Day 28.

Secondary endpoints

The following efficacy endpoints were evaluated in the study population overall and by GVHD grade, where appropriate:

- Overall response rate (CR or PR) through Day 100
- Complete response rate through Day 100
- Response by organ
- Effect of continuing therapy.

7.1.2.6. Randomisation and blinding method

This was a single-arm study. Consequently, the study was not randomised or blinded.

7.1.2.7. Analysis populations

The efficacy and safety populations included all patients who had received at least 1 dose of Prochymal.

7.1.2.8. Sample size

There was no sample size determination for statistical power performed for this study.

7.1.2.9. Statistical methods

The study employed standard statistical descriptive methods. Missing organ stage was not imputed as the GVHD assessment should have been staged completely for all organs. Missing

GVHD assessment at a post-Baseline visit was imputed with an end-of-treatment assessment if it occurred within 3 days of the post-baseline visit date. The first time point of response was changed from Day 32 to Day 28 in the revision of the original protocol in Amendment 1. For patients enrolled under the original protocol, the Day 32 visit data were used for the Day 28 assessments dictated in the SAP. Visit windows were as specified in the protocol.

7.1.2.10. Participant flow

The study enrolled 59 patients, and all 59 were included in the efficacy population (i.e., received at least one study infusion of Prochymal). Of the 59 enrolled patients, 22 (37.3%) died before the end of the study (day 100). Subjects who died during the study were considered to have completed the study unless the subject discontinued prior to death. Of the 59 enrolled patients, 58 (98.3%) completed the study by 30 December 2009, and 1 (1.7%) did not complete the study and discontinued due to a serious adverse event (acute respiratory distress).

7.1.2.11. Major protocol deviations

The most common protocol deviations were for Day 28 and Day 100 assessments performed outside of protocol specified window, and vital signs, CT scans, and ECGs not performed as specified in the protocol. Additionally, for some patients, due to their young age, pregnancy tests were not performed as specified in the protocol. Two paediatric patients did not meet the inclusion criteria but were still enrolled: 1 had a possible pork allergy, and 1 was considered by the Investigator to have failed steroid therapy although the steroid dosing did not meet the inclusion criteria. Waivers to have an infusion administered before the required exclusionary window of 3 days between infusions were granted to 4 patients The last infusion after Day 100 was administered to 3 patients. There was 1 patient who received a dose of Prochymal with a viability of 55%. There were 5 who continued to receive treatment after Day 28, but source data verification established that they had Day 28 responses (CR or NR) and were not eligible for continued treatment.

7.1.2.12. Baseline data

The baseline demographic data for the safety population are summarised below in Table 6. Baseline is defined as the last observation prior to the first infusion, including screening where applicable.

Table 6: Protocol 275 – Demographic and baseline characteristics; safety population

Age (n=59)	Mean ± sd = 8.4 ± 5.97 years; Median (range) = 7.8 (0.2, 17.5) years.
Male / Female	36 (61.0%) / 23 (39.0%)
Race (n=59)	34 (57.6%) White; 12 (20.3%) African-American; 5 (8.5%) Asian; 1 (1.7%) American Indian or Alaskan Native; and 7 (11.9%) were reported as "other."
Height (n=52)	Mean ± sd = 120.8 ± 39.05 cm; Median (range) = 123.1 (12.1, 178.6) cm.
Weight (n=59)	Mean ± sd = 32.4 ± 21.53 kg; Median (range) = 26.9 (5.4, 103.7) kg.

Notes: Age calculated from day of enrolment.

Of the 59 patients, 37 (62.7%) were transplanted for haematological malignancies and 22 (37.3%) were transplanted for non-malignant diseases, primarily of genetic origin. The most common underlying malignancies or leukemic diseases at transplant were acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) with 14 patients (23.7%) each, followed by 'Other' with 13 patients (22.0%) which included 4 subjects with genetic diseases, and genetic disease with 11 patients (18.6%). Of the 59 patients, the donor was unrelated for 49 (83.1%) of the transplantations and related for 10 (16.9%). Donor compatibility was 52.5% matched for 31 (52.5%) patients and unmatched for 28 (47.5%) patients. The HSCT source was bone marrow for 19 patients (32.2%), PBSC for 13 patients (22.0%), cord blood for 22 (37.3%) patients, and DLI for 4 (6.8%) patients.

The mean±SD time from HSCT to GVHD onset was 50.7± 54.2 days (median: 29.0 days). At onset, GVHD was severe (Grade C or D) in the majority of patients (n=42, 71.2%), with Grade A being reported in 6 (10.2%) patients and Grade B in 10 (16.9%) patients. At baseline, 7 patients (11.9%) had GVHD Grade B, 17 patients (28.8%) had GVHD Grade C, and 35 patients (59.3%) had GVHD Grade D (i.e., 88.1% of patients had severe or very severe disease Grade C/D at baseline).

Gastrointestinal (GI) involvement was present in 52 (88.1%) patients, with 32 (54.2%) having Stage 4 (maximum) involvement. Skin involvement was present in 33 (55.9%) patients, and liver involvement was present in 21 (35.6%) patients. Two organs were involved in 27 (45.8%) patients, and all three organs were involved in 10 (16.9%) patients. Of the 22 patients with single organ involvement, 15 (68.2%) had GI involvement.

The majority (61.0%) of patients had received 2 or more additional agents after failing steroids (i.e., a total of at least three prior therapeutic agents for GvHD one of which included steroids). There were 11 (18.6%) patients enrolled in the study after failing systemic steroids only, and 12 (20.6%) patients after receiving 1 agent in addition to systemic steroids. The most common previously attempted second-line GVHD agents were infliximab (n=32, 54.2%), tacrolimus (n=26, 44.1%), mycophenolate mofetil (n=16, 27.1%), and daclizumab (n=16, 27.1%).

The mean ± SD time from GVHD onset to start of treatment with Prochymal was 75.5 ± 213.29 days (median: 30.5 days, range 2-1639 days). The large SD for the time to onset was primarily due to a single patient who started treatment 1639 days after being diagnosed with GVHD, and the Investigator specifically stated that this patient met the criteria for acute GVHD. When this patient was excluded, the mean ± SD time of onset of GVHD to initiation of Prochymal was 48.7 ± 43 days.

There were 58 patients with information relating to GVHD response before initiation of Prochymal. Of these 58 patients, 38 (65.5%) had worsening disease GVHD (grade increasing) or had maximal GVHD (grade D at both GVHD onset and baseline), 18 (31.0%) were unchanged (no change in GVHD grade), and 2 (3.4%) were improving (at least 1 letter grade reduction in GVHD). The 56 (96.6%) patients who were not improving (i.e., GVHD unchanged; or GVHD worsening or maximal GVHD present) had been receiving treatment for GVHD for a median of 30.5 days. Of the 59 enrolled patients, 45 (76.3%) had received no second line treatment within 1 week prior to study treatment, and 14 (23.7%) had started second line study treatment within 1 week prior to study treatment.

7.1.2.13. Results for the primary efficacy outcome

The primary efficacy endpoint was overall response (OR = CR + PR) at Day 28 (Table 7). Day 28 includes assessments between study days 20 and 38. Patients who died on or before study day 28 are considered non-responders.

Table 7: Protocol 275 – Overall response (CR + PR) to Prochymal at Day 28; 59 patients

	Overall GVHD B-D (n=59)	GVHD Grade B (n=7)	GVHD Grade C (n=17)	GVHD Grade D (n=35)
Responder	**37 (62.7%)**	5 (71.4%)	13 (76.3%)	19 (54.3%)
Non-Responder	**22 (37.3%)**	2 (28.6%)	4 (23.5%)	16 (45.7%)

Notes: (1) GvHD grade is from the Baseline assessment. (2) Responder is defined as a subject with an overall response (complete response or partial response) at Day 28. (3) Day 28 includes assessments between study days 20 and 38. Patients who died on or before study day 28 are considered non-responders. (4) Subject 005/002 is counted as a non-responder because he received an infusion of Prochymal but died on Study Day 9 prior to any additional assessments.

> **Comment:** The protocol specified that primary efficacy endpoint of OR was to be assessed at Day 28 ± 2 days. However, the provided results for the OR at Day 28 included assessments undertaken between study days 20 and 38. In the original protocol (i.e., prior to amendment), assessment of the OR was to be undertaken at Day

32 ± 2 days, and for patients treated under the original protocol Day 32 visit data were used for the Day 28 assessments. No data could be identified in Protocol 275 for the OR rates of those patients who were assessed at the pre-specified time interval of 28 ± 2 days. The inclusion of patients assessed between study days 20 and 38 in the OR at Day 28 ± 2 days analysis is considered to be a major protocol deviation, and potentially overestimates the response to Prochymal.[3]

The reported OR rate at 28 days (range 20 to 38 days) was greater than the overall non-responder rate. The differences between responders and non-responders in the overall population (Grade B/C/D) were driven primarily by the GVHD Grade C results. There was a smaller absolute difference between the proportion of responders and non-responders in patients with CVHD Grade D (the most severe category) compared with patients with GVHD Grade C. In the overall population (Grade B/C/D), the absolute difference between responders and non-responders was 15 patients consisting of 9 (60%) patients from the GVHD Grade C group, and 3 (20%) patients from each of the GVHD Grade B and D groups.

7.1.2.14. Results for other efficacy outcomes

Secondary efficacy endpoints

Overall response (OR = CR + PR) rate through to Day 100

In the overall GVHD Grade B-D group (n=59), there were 47 (79.7%) responders and 12 (20.3%) non-responders. The corresponding results (responders vs non-responders) for the individual groups were: GVHD Grade B (n=7), 7 (100%) vs 0; GVHD Grade C (n=17), 15 (88.2%) vs 2 (11.6%); and GVHD Grade D, 25 (71.4%) vs 10 (28.6%).

Complete response (CR) rate through to Day 100

In the overall GVHD Grades B-D group (n=59), there were 22 (37.3%) responders and 37 (62.7%) non-responders. The corresponding results (responders vs non-responders) for the individual groups were: GVHD Grade B (n=7), 5 (71.4%) vs 2 (28.6%); GVHD Grade C (n=17), 8 (47.7%) vs 9 (52.9%); and GVHD Grade D , 9 (25.7%) vs 26 (74.3%).

Response by organ involvement

The response to Prochymal treatment by organ involvement was evaluated according to the IBMTR organ staging scheme. The changes in GVHD organ stage data from Baseline to Day 28 were displayed in shift tables for skin, GI, and liver. In addition, the response by organ was also summarised as improving (reduction by at least 1 stage), stable (no change in the stage), progressing (an increase by at least 1 stage), or death.

- Skin involvement: Overall, 25 (75.8%) of the 33 patients with skin GVHD at Baseline (stage > 0) had improvement in their skin disease at Day 28, with complete resolution occurring in 13 (39.4%) patients; 4 (12.1%) patients had stable skin disease; 4 (12.1%) patients had died by Day 28; and no patients experienced progression of skin disease from baseline. Of the 25 patients without skin GVHD disease at baseline, 2 (8.0%) had developed GVHD involving the skin at Day 28.
- Lower GI involvement: Overall, 31 (59.6%) of the 52 patients with GI GVHD at Baseline (stage > 0) had improvement in their GI disease at Day 28, with complete resolution occurring in 15 (28.8%) patients; 12 (23.1%) patients had stable lower GI disease; 7 (13.5%) patients with lower GI involvement at baseline died by Day 28; 2 (3.8%) patients with lower GI GVHD at baseline experienced progression of the GI disease. Of the 7 (14.3%) patients without lower GI GVHD at baseline, 1 (14.3%) had developed GVHD involving the lower GI at Day 28.

[3] See also Clinical questions, Efficacy Question 1 below.

- Liver involvement: Overall, 11 (52.4%) of the 21 patients with liver GVHD at Baseline (stage > 0) had improvement in their liver disease at Day 28, with 9 cases (42.9%) completely resolving; 5 (23.8%) patients had stable disease of the liver; 4 (19.0%) patients with liver involvement at baseline died by Day 28; 1 (4.8%) with liver GVHD at baseline experience progression of the liver disease. Of the 37 patients without liver GVHD at baseline, 3 (8.1%) had developed GVHD involving the liver at Day 28.

Effect of continuing therapy

To assess the effect of continuing therapy in patients who received additional Prochymal (> 8 infusions) response from Day 28 to Day 100 was summarised by changes in GVHD grading and/or staging. For a patient to be considered a responder to continuing therapy, they must have experienced additional improvement in at least 1 organ, of at least 1 stage without worsening in any other organ from Day 28 to Day 100. Patients who maintained a CR after Day 28 were also considered responders. Patients who had a PR at Day 28, but had no change in organ staging between Day 28 and Day 100, were considered non-responders.

Overall, 33 (55.9%) of 59 patients with GVHD (B-D) at baseline received > 8 Prochymal infusions and were included in the continuing therapy analysis. Of these 33 patients, 18 (54.5%) were responders as they experienced additional benefit from continuing therapy. Of the 18 responders, 2 were complete responders who maintained their response through Day 100, and the other 16 showed additional improvement in their GVHD (and 12 achieved a CR). When stratified by baseline GVHD grade: 3/5 Grade B patients (60.0%) experienced additional benefit; 9/11 Grade C patients (81.8%) experienced additional benefit; and 6/17 Grade D patients (35.3%) experienced additional benefit.

Other endpoints (not pre-specified as primary or secondary efficacy endpoints)

Overall response at day 28 with respect to addition of second-line agents

The OR at Day 28 in patients with no second-line and with second-line GVHD agents started within 1 week prior to study Prochymal were similar (62.2% and 64.3%, respectively). These results suggest that treatment with second-line agents started within 1 week prior to Prochymal did not significantly affect the overall response rate at Day 28.

Survival to 100 days – OR responders and non-responders at Day 28

Of those patients with an OR at Day 28, 75.7% (29/37) survived at least 100 days past the first infusion, while in those patients without an OR at Day 28 the corresponding survival rate was 31.8% (7/22). The log-rank test for the comparison of survival probability for responders versus non-responders demonstrated a significant 100-day survival advantage for those patients with an OR at Day 28 (78% vs 36%, respectively, $p < 0.001$). Two patients (one a responder and the other a non-responder) that were not confirmed dead, but who completed the study prior to Day 100 (Day 92 and Day 99), were censored.

Survival through to 180 days following onset of GVHD

The overall survival at 180 days following onset of GVHD was 62.1% (36/58). Kaplan-Meier survival analysis showed that the probability of survival at 180 days in the overall population (n=58) was 65.2% [95% CI: 52.9, 77.5].

The submission included a comparison between the Kaplan-Meier probabilities of 180 day survival for patients in Protocol 275 and a historical control (external benchmark) of paediatric patients with acute GVHD Grade II-IV from the CIBMTR database. The survival analysis of the CIBMTR data was performed independently by that organisation and the results compared with the analysis of the data from Protocol 275. These patients were transplanted in the US, Canada, and European Union from 1997-2006, had developed maximum grade II-IV acute GVHD, and had received additional treatment for GVHD in addition to systemic steroids.

The comparison between the historical control (CIBMTR) and Prochymal (Protocol 275) showed that the probabilities of 180 day survival for patients with maximum GVHD Grade C were 69.0% [95% CI: 64.0, 74.0] and 87.1% [95% CI: 70.3, 100], respectively, and for patients with maximum GVHD Grade D were 31.0% [95% CI: 26.0-36.0] and 56.2% [CI: 40.5-71.8], respectively. Patients who had received Prochymal had a statistically significantly higher probability of survival compared with the historical control (CIBMTR) patients (p=0.003).

> **Comment:** The sponsor acknowledged a number of limitations with the CIBMTR benchmark population. These included: not all patients may have been steroid refractory; the diagnosis of steroid refractory acute GVHD was not confirmed in the clinical reports, and physicians may have used second-line therapy before steroid refractory acute GVHD was diagnosed; only the maximum Grade during the course of the disease was collected, resulting in bias towards the most severe Grade (D); and the CIBMTR data overstates the degree of severity (specifically organ involvement) relative to Protocol 275 due to maximum Grade during the treatment period being recorded rather than maximum Grade at a specific time point.

7.1.3. Other efficacy studies: Paediatric single patient emergency use protocols

7.1.3.1. Overview

The submission included a clinical summary report (BB-IND No. 7939-Prochymal) titled – 'Pediatric Single-Patient, Emergency-Use Protocols to Evaluate the Safety and Treatment Outcomes of Prochymal ... Infusions for the Salvage of Treatment Refractory Acute GVHD Patients'.

The objectives of these protocols were to treat patients on a compassionate basis, and to assess the safety and treatment outcomes of Prochymal administered to patients with acute GVHD (Grades III or IV or C or D) refractory to standard first line therapies and at least one second-line therapy.

The report was dated 24 May 2010. It summarised the response and safety outcomes from 12 patients administered Prochymal between 25 July 2005 (first patient) and 26 December 2007 (last patient). The studies (i.e., individual protocols) were performed at multiple sites, each with its own Principal Investigator. There were 5 clinical centres in the US that enrolled patients, and 7 investigators who treated the enrolled patients. The report states that the study was 'completed according to the guidelines of Good Clinical Practice. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial patients are protected, consistent with the principles that have their origin in the Declaration of Helsinki'.

7.1.3.2. Treated patients

The 12 paediatric patients (aged between 6 and 17 years) included in the report had acute GVHD Grades C-D or III-IV that had failed to respond to steroids and other immunosuppressive therapies. Of the 12 patients, 6 (50%) completed the Day 100 and Day 180 visits; 1 (8.3%) discontinued (withdrew consent); and 6 (50%) died on or before the 100 Day visit.

7.1.3.3. Treatment protocols

The 12 patients were treated under one of three separate protocols, following physician requested 'compassionate' treatment approved by the relevant site specific IRB. The sponsor (Osiris) sent the physician's request, medical summary of the patient and the treatment plan to the United States Food and Drug Administration (FDA) for approval of each protocol.

The three treatment protocols are outlined below (208, 215-231, 270E.8). For patients weighing ≥ 35 kg, Prochymal was administered iv at a controlled rate of 4-6 mL/minute via an infusion pump. For patients weighing < 35 kg, Prochymal was infused over the course of 60 minutes. A syringe in combination with a syringe pump may have been used for administration of Prochymal to patients under 35 kg.

- Protocol 208: The treatment plan for Protocol 208 (the initial protocol) included two iv infusions of Prochymal at a dose of 8 x 10^6 hMSC/kg (actual body weight). The treating physician also had the option to administer up to an additional six infusions at a dose of 8 x 10^6 hMSC/kg within the first six months of the study. Additional GVHD therapies were administered in combination with the continued Prochymal treatments as per institutional guidelines. The Prochymal dose and treatment regimen in this protocol was notably different from that being proposed for approval.
- Protocols 215-231: The initial treatment plan for Protocols 215 to 231 included 8 iv infusions of Prochymal at a dose of 2 x 10^6 hMSC/kg (actual body weight). Infusions were to be administered twice per week (at least three days apart) for four consecutive weeks. A therapy assessment was to be performed on Day 32 (±2 days) post-first infusion to determine whether continued treatment was indicated. Patients who had a partial or mixed response were eligible for continued treatment and the treating physician administered Prochymal at a dose of 2 x 10^6 hMSC/kg once per week for an additional 4 weeks. Additional GVHD therapies were administered in combination with the continued Prochymal treatments as per institutional guidelines. The Prochymal dose and treatment regimen in these protocols were consistent with that being proposed for approval.
- Protocol 270E.8: The initial treatment plan for Protocol 270E.8 included a minimum of one iv infusion of Prochymal at a dose of 8 x 10^6 hMSC/kg (actual body weight). The treating physician had the option to administer up to a total of 8 infusions within a 28-day study period. Additional GvHD therapies were administered in combination with the continued Prochymal treatments as per institutional guidelines. The Prochymal dose and treatment regimen in this protocol was notably different from that being proposed for approval.

7.1.3.4. Response criteria and outcomes

- Survival was assessed in all single-patient, emergency-use protocols.
  - There were 6 (50%) patients who survived through Day 100 following the first infusion of Prochymal; the mean ± SD and median (range) survival times of patients who died on or before Day 100 were 63 ± 24 days, and 55 (36-100) days, respectively.
  - There were 6 (50%) patients who survived through Day 180 following the first infusion of Prochymal; mean and median survival times of patients who died or before Day 180 were the same as those who died on or before Day 100.
  - There were 9 (75%) patients who survived through 180 Days following HSCT.
- Best Overall Response (Complete or Partial Response) was assessed in all single-patient, emergency use protocols.
  - Overall response (CR + PR) was achieved in 66.7% (8/12) of patients; CR = 4/12 (33.3%) + PR = 4/12 (33.3%).
  - Mixed response was achieved in 25% (3/12) of patients; mixed response was defined as improvement in at least one evaluable organ with worsening in another.
  - No response (stable or worsening disease) was observed in 1 (8.3%; 1/12) patient.
  - There were 4/12 (33.3%) non-responders (i.e., subjects not achieving an OR).
- Response by Day 28 was assessed only in Protocol 270-E.8.
  - The one patient in this protocol had a partial response at Day 28 (i.e., acute GVHD grade changed from IV at baseline to III by Day 28).

7.1.4. Analyses performed across trials

There were no formal analyses performed across trials (i.e., pooled analyses and meta-analyses). This is considered to be acceptable as pooling the paediatric data from Protocols 280

and 275 would have been methodologically unsound due to the difference in study design between these two protocols.

7.1.5. Evaluator's conclusions on clinical efficacy for steroid refractory acute GVHD

7.1.5.1. Overall comments

It is considered that the submitted data do not support the efficacy of Prochymal for the rescue of patients ≥ 6 months of age with acute GVHD refractory to treatment with systemic corticosteroid therapy or other immunosuppressive agents. The pivotal study is considered to be Protocol 280, and the analyses of the primary and secondary efficacy endpoints in this study showed no statistically or clinically significant differences between Prochymal and placebo. The study was multi-national, multi-centre, randomised, placebo-controlled and double-blind in design and included a total of 260 patients analysed for efficacy across the age range covered by the proposed indication. The mean ± SD age of patients in the study was 42.6 ± 17.2 years, and the majority of patients were aged ≥ 18 years (89.2%; n=232).

The supportive study is considered to be Protocol 275, a multi-national, multi-centre, Prochymal single-arm study in 59 paediatric patients aged < 18 years (mean±SD age 8.4±6.0 years, range 0.2 to 17.5 years). However, the data from this study is considered to be difficult to meaningfully interpret due to the absence of a placebo-control arm. Therefore, protocol 275 is considered to provide inadequate evidence supporting the efficacy of Prochymal for the proposed indication in the proposed population. The efficacy data from the CSR (BB-IND No. 7939-Prochymal) relating to 12 paediatric patients treated under single-patient, emergency-use protocols are of interest only, and are not considered to be relevant to the regulatory decision to approve or reject the application to register Prochymal for the proposed indication.

In documents submitted by the sponsor, Protocol 275 was nominated as the pivotal study, although it included only paediatric patients aged less than 18 years. From the content of the Clinical Overview, and the Clinical Efficacy and Safety Summaries, it appears that the submission was primarily prepared to support Prochymal for rescue treatment of steroid refractory acute GVHD in a paediatric population (i.e., patients aged < 18 years) rather than in both paediatric and adult populations (as proposed for Australia). For the purposes of the Australian submission, Protocol 275 should be considered to be supportive rather than pivotal as it does not include the complete age range of patients proposed for treatment with Prochymal covered by the proposed Australian indication.

Protocol 275 was a single-arm study, and the absence of a placebo control arm makes interpretation of the data difficult. Osiris stated that Protocol 275 did not include a placebo-control for 'ethical reasons', and instead a 'historical control was employed for the comparison of survival'. The historical control was used to evaluate the 180 day survival data, and there was no historical control to aid evaluation of the pre-specified primary and secondary efficacy endpoints. In Protocol 280, the choice of the placebo control group was justified by the sponsor because both active and placebo treatment groups also received the institutionally defined standard of care (e.g., a second-line therapy in addition to continued corticosteroid treatment). However, Protocol 275 also allowed standard supportive therapy for GVHD to be administered at the Investigator's discretion and in accordance with site-specific policies. As discussed above, it appears to be inconsistent to state that a placebo control was not considered to be an option for 'ethical reasons' in Protocol 275, but was permitted in Protocol 280. There is information in the submission suggesting that Protocol 275 was initiated at the request of physicians who specifically wanted to treat their patients with Prochymal rather than enrol them in Protocol 280 and risk randomisation to placebo.

The difficult of interpreting the results of the Protocol 275 without a placebo control can be illustrated by examination of the primary efficacy endpoint in this study of overall response at Day 28. The overall response rate at Day 28 in Protocol 275 was 62.7% (37/59) and the non-responder rate was 37.3% (22/59). In Protocol 275 it is stated that 'due to the refractory nature

of this population [i.e., patients with acute GVHD refractory to corticosteroids] achieving any response in these patients is meaningful and unexpected' (CSR, Section 11.4.9). However, the overall response rate at Day 28 in Protocol 280 was 57.7% (94/163) in the Prochymal group compared with 50.6% (41/81) in the placebo group, p=0.224. Consequently, from the Protocol 280 results it can be concluded that a meaningful overall response at Day 28 was obtained not only for patients treated with Prochymal, but also for those who received placebo. Therefore, it is considered that the results for overall response at Day 28 from Protocol 280 do not support the statement in Protocol 275 that any response to Prochymal in patients with acute GVHD refractory to corticosteroids is 'meaningful and clinically unexpected'. Furthermore, in Protocol 275 the OR at Day 28 was based on patient assessments between study days 20 and 38 rather than 28 ± 2 days as specified in the protocol. Consequently, the reported OR at 28 days in Protocol 275 might be an overestimation of the protocol specified response.

The difficulty of interpreting the results of Protocol 275 without a placebo control can be further illustrated by examination of the 180 day survival data. In Protocol 275, patients treated with Prochymal had a statistically significantly higher probability of survival through to 180 days (post onset of aGVHD) compared with patients in the historical control group (p=0.003). The effect size was most pronounced in the acute GVHD Grade D population (historical control: 31.0% [95% CI: 26.0-36.0] vs Prochymal: 56.2% [CI: 40.5-71.8]). However, in Protocol 280, survival > 180 days (post study start) in the overall acute GVHD (Grade B-D) population was higher in the placebo group than in the Prochymal group (42.0% [34/81] vs 34.4% [56/163], respectively; p=0.274). Furthermore, in Protocol 280 the corresponding results for the acute GVHD (Grade C/D) population was 30.2% (28/126) in the Prochymal group and 40.0% (24/60) in the placebo group.

Despite the Protocol 275 results on the 180 day (post onset of aGVHD) survival data showing significant superiority of Prochymal compared with a historical control, the Protocol 280 results did not show the same effect at a later point in the disease course. In considering the survival data in Protocol 280 Osiris concluded that, 'once past the treatment phase and especially beyond Day 100, there are many competing risks for this severely ill patient population with a life-threatening disease, which cannot be controlled within the framework of a clinical trial. These confounding factors make it difficult to evaluate survival at later times'.

7.1.5.2. Protocol 280

In Protocol 280, there was no statistically significant difference between Prochymal and placebo for the pre-specified primary efficacy endpoint of complete response sustained for ≥ 28 days in the ITT population: 34.7% (60/173) and 29.9% (36/87), respectively, p=0.423. The study was powered on a complete response rate of 29% in the placebo group and 49% in the Prochymal groups. Consequently, it can be inferred that the absolute difference of 4.8% between the Prochymal and placebo groups observed for complete response sustained for ≥ 28 days is clinically non-significant. In addition, there were no statistically or clinically significant differences between Prochymal and placebo for the pre-specified secondary efficacy endpoints in the mITT population of survival post-infusion for greater than 100 days (52.1% vs 50.6%, respectively, p=0.780), and for greater than 180 days (34.4% vs 42.0%, respectively, p=0.274). There were also no clinically meaningful differences between the two treatment groups in average corticosteroid use from post infusion through to day 56 computed at weekly intervals (descriptive statistics only presented). Overall, the analyses of the pre-specified primary efficacy endpoint (complete response rate sustained for a duration of ≥ 28 days) and secondary efficacy endpoints (survival status at 100 and 180 days) are considered to be robust, and unequivocally demonstrate that the observed differences between Prochymal and placebo are not statistically or clinically significant.

Despite the robust primary and secondary efficacy endpoint analysis demonstrating no significant difference between Prochymal and placebo Osiris states that 'given the inherent challenges associated with conducting a large, controlled trial in steroid refractory GvHD, these

analyses [the additional and/or exploratory efficacy analyses discussed below] provide placebo-controlled evidence that Prochymal results in a clinical benefit to patients with visceral organ steroid-refractory GvHD'. In coming to this conclusion the sponsor appears to give more weight to the evidence from additional and/or exploratory efficacy analyses than to the pre-specified primary and secondary efficacy analyses. This approach is considered to be unacceptable for the regulatory purpose of determining whether Prochymal should be approved for the proposed usage in the proposed patient population. From a regulatory perspective, it is considered to be methodologically unsound to emphasise the importance of the efficacy results from additional and/exploratory endpoint analyses when the pre-specified primary and secondary efficacy analyses unequivocally fail to demonstrate the significance of the investigational agent compared with placebo.

In discussing the efficacy conclusions, Osiris states that the study 'had a rigorous primary endpoint - a complete response, meaning complete resolution of all clinical signs of GVHD - that had to be maintained for at least 28 consecutive days'. While mentioning that the outcome of the pre-specified primary efficacy analysis 'did not reach significance', the CSR goes on to state, ' [h]owever, for patients who received treatment according to the trial design, the Per Protocol population, Prochymal outperformed placebo 40% versus 28% (p=0.087), essentially in-line with the original protocol assumptions'. However, the PP analysis was defined in the SAP for Protocol 280 as 'an exploratory analysis', with the ITT analysis being defined as the primary efficacy analysis. Furthermore, the difference between the two treatment groups as regards the analysis of the pre-specified primary efficacy endpoint in the PP population was not statistically significant, and the absolute of difference of 12% between the two treatment groups is not clinically significant (based on the 20% difference specified in the sample size calculations). Furthermore, relevant TGA adopted guidelines recommend the ITT population rather than the PP population as the preferred population for analysis of efficacy as it maintains the benefits of randomisation and is less subject to bias than the PP population (see TGA adopted document 'Note for Guidance on Statistical Principles for Clinical Trials', ICH Topic E9). Consequently, for regulatory purposes it is considered that the Protocol 280 results of the primary efficacy analysis in the ITT population should be given more weight than the results from the 'exploratory' analysis in the PP population.

Osiris also states that 'a similarly impressive effect size [to that observed in the PP for complete response for a duration of ≥ 28 days] was observed in those patients who had more steroid refractory disease, indicated by being on steroids longer than 14 days prior to study entry. In this population [ITT], 38% [24/64] of Prochymal patients had a DCR compared to only 21% [5/29] of placebo'. No statistical analysis was provided for this endpoint and the results were summarised descriptively. Furthermore, this efficacy endpoint appeared to have been defined post-hoc as it could not be identified in the SAP for Protocol 280.[4]

Osiris stated that 'the immediate goal of treatment is to stop progression of disease and to introduce a clinically meaningful response as quickly as possible', and referred to the 'Overall Response' data as providing 'further support' for 'the efficacy of Prochymal to enhance response in steroid refractory GVHD and provide immediate clinical benefit to the patient. An OR reflects an objective reduction of a patient's symptoms, which are severe in GVHD. Therefore, OR is itself a direct measure of clinical benefit. At Day 28, Prochymal outperformed placebo 58% to 51%. The improvement with Prochymal was statistically significant by Day 100, with 82% OR for Prochymal and 72% OR for placebo (p=0.034)' (CSR, Section 11.4.4). It was further stated that, 'the effect of Prochymal [OR at days 28 and 56] was significantly greater when treating GVHD involving visceral organs (liver and GI tract) than skin'. However, it should be noted that the ORs for each organ at Day 28 and Day 100 in the mITT were pre-specified as 'additional efficacy variables' (i.e., neither primary nor secondary efficacy variables). The OR rates at Day 28 and

[4]The analysis was predefined.

100 for the skin were similar in the Prochymal and placebo groups, the OR rates for the lower GIT were higher in the Prochymal group than in the placebo group at Day 28 (not statistically significant) and Day 100 (statistically significant), and the OR rates for the liver were statistically significantly higher in the Prochymal group than in the placebo group at both time-points.

Osiris stated that 'once past the treatment phase and especially beyond Day 100, there are many competing risks for this severely ill patient population with a life-threatening disease, which cannot be controlled within the framework of a clinical trial. These confounding factors make it difficult to evaluate survival at later times'. In an additional analysis in the mITT performed to evaluate survival while on treatment (i.e., through to Day 56), survival > 56 days was higher in the Prochymal group (67.5%, n=110) than in the placebo group (59.3%, n=48) (p-value not provided). The difference in survival in the overall population (liver, lower GI, skin) were primarily driven by the differences between the two treatment groups in patients with liver and lower GI involvement. In patients with liver involvement, overall survival > 56 days was 57.1% (n=24) for Prochymal treated patients and 26.3% (n=5) for placebo patients, for patients with lower GI involvement the respective figures were 63.5% (n=73) and 50.8% (n=30), and for patients with skin involvement the respective figures were 66.3% (n=61) and 63.5% (n=33).

Osiris stated that that the results of Protocol 280 supports 'OR at Day 28 as a clinically meaningful endpoint, especially for patients with visceral organ involvement who have very poor outcomes'. In addition, it was stated that OR can also serve as a surrogate endpoint by improving the chances of survival, and reference was made to 'an ad hoc analysis of survival data [which] showed the probability of survival at Day 100 was 71% for patients who attained OR and 32% for non-responders ... supporting the clinical significance of the endpoint ($p<0.001$, Log-Rank test)'. However, at Day 28, while the OR in the Prochymal group was higher than in the placebo group the difference between the two treatment groups was not statistically significant (57.7% [94/163] and 50.6% [41/81], respectively; p=0.224). In addition, the actual observed overall survival > 100 days did not significantly differ between the treatment groups in the mITT population (Prochymal 52.1% vs placebo 50.6%; p=0.780). Furthermore, the OR at Day 28 was not pre-specified in Protocol 280 as either a primary or secondary efficacy endpoint, and this endpoint appeared to be a post-hoc consideration.

7.1.5.3. Protocol 275 (paediatric patients)

Protocol 275 was a Prochymal single-arm study in 59 enrolled paediatric patients aged younger than 18 years (mean ± SD age 8.4 ± 5.97 years, range 0.2 to 17.5 years). At baseline, 88.1% of enrolled patients had severe or very severe acute GVHD (Grade C/D), 62.7% had received a donor unrelated transplantation, 52.5% were compatibility matched with the donor, and 61% had received prior treatment with two second line-agents in addition to systemic steroids.

As discussed above, the absence of a placebo control group makes the results of this study difficult to interpret. The primary efficacy endpoint was the OR (CR + PR) at Day 28 and was observed to be 62.7% (37/59), but assessment could have taken place from day 20 to day 38. Osiris states that 'due to the refractory nature of this population, achieving any response in these patients is meaningful and largely unexpected'. However, as discussed above, the OR results at Day 28 from Protocol 280 in the Prochymal and placebo groups raises doubts about the validity of this statement.

The study included 4 secondary efficacy endpoints (overall response rate through Day 100, complete response rate through Day 100, response by organ involvement, and effect of continuing therapy). The OR rate through Day 100 was greater than the non-response rate in the acute GVHD Grade B-D population (79.7% vs 20.3%), but conversely the CR rate through Day 100 was lower than the non-response rate (62.7% vs 37.3%). Improvement in disease status as defined by at least 1 stage reduction from baseline to Day 28 in patients with organ involvement at baseline (stage > 0) was observed in 25 of the 33 patients (75.8%) with skin

GVHD, 31 of the 52 patients (59.6%) with lower GI GVHD, and 11 of the 21 patients (52.4%) with liver GVHD. Overall, 33 of 59 (55.9%) patients received > 8 Prochymal infusions and were included in the continuing therapy analysis. Of these 33 patients, 18 (54.5%) experienced an additional benefit from therapy, defined as experiencing a least a partial response from Day 28 to Day 100.

8. Clinical safety

8.1. Studies providing evaluable safety data

In this CER, the safety data from Protocol 280 (adult and paediatric patients) and Protocol 275 (paediatric patients) have been reviewed separately. It is considered that Protocol 280 includes the most informative safety data as it included randomised, double-blind, Prochymal and placebo treatment groups in patients aged 6 months to 70 years, inclusive. The submission included a Summary of Clinical Safety (SCS) that focused on the paediatric safety data from Protocol 280 (Prochymal, n=14 and placebo, n=14), Protocol 275 (Prochymal, n=59), and single-patient, emergency-use protocols (Prochymal, n=12).

8.2. Pivotal studies that assessed safety as a primary outcome

8.2.1. Protocol 280

8.2.1.1. Exposure

In Protocol 280, all safety analyses were undertaken in the safety population defined as all randomised patients who received at least 1 dose of Investigational Agent. There were 260 randomised patients, and 244 (93.8%) of these patients were included in the Safety Population (Prochymal, n=163 [94.2%]; placebo n=81 [93.1%]).

Patients treated with Prochymal had marginally greater drug exposure as measured by number of infusions, cumulative dose, and days of exposure than patients receiving placebo. The mean ± SD total cumulative dose was 17.7 ± 6.1 x 10^6 hMSC/kg in the Prochymal group and the equivalent infusion volume in the placebo group was 16.2 ± 6.1 x 10^6 hMSC/kg. The mean ± SD extent of exposure was 36.0 ± 18.6 days for Prochymal and 31.7 ± 17.5 days for placebo. In the Prochymal group, 39.9% of patients received more than 8 infusions compared with 32.1% of patients in the placebo group.

8.2.2. Adverse events

8.2.2.1. All adverse events irrespective of relationship to treatment

Treatment emergent adverse events (TEAEs) were defined as any AE occurring during the study from the start of the first infusion (Day 0) until completion of the end-of-study procedures. All patients experienced at least 1 TEAE during the study, with a total of 3165 TEAEs being reported for the 163 patients in the Prochymal group, and 1376 TEAEs being reported for the 81 patients in the placebo group.

The most commonly reported System Organ Class (SOC) disorders occurring in at least 40% of patients in either group (Prochymal vs placebo) were: Infections and Infestations (88.3% and 81.5%); Gastrointestinal Disorders (74.2% and 77.8%); General Disorders and Administration Site Conditions (68.1% vs 69.1%); Metabolism and Nutrition Disorders (67.5% vs 48.1%); Respiratory, Thoracic and Mediastinal Disorders (62.0% vs 59.3%); Psychiatric Disorders (54.6% vs 37.0%); Investigations (49.7% vs 45.7%); Blood and Lymphatic System Disorders (45.4% vs 34.6%); Skin and Subcutaneous Tissue Disorders (43.6% vs 35.8%); Nervous System Disorders (41.1% vs 46.9%); Musculoskeletal and Connective Tissue Disorders (42.3% vs 44.4%); and Renal and Urinary Disorders (39.9% vs 40.7%).

The reported SOCs (HLT and PT) occurring in at least 10% more patients in the Prochymal group than in the placebo group were: Metabolism and Nutrition Disorders 19.4% (67.5% vs 48.1%); Psychiatric Disorders 17.6% (54.6% vs 37.0%); Cardiac Disorders 10.9% (34.4% vs 23.5%); and Blood and Lymphatic System Disorders 10.8% (45.4% vs 34.6%). There were no reported SOCs (HLT and PT) occurring in at least 10% more patients in the placebo group than in the Prochymal group.

The most commonly reported TEAEs occurring in ≥ 20% of patients in either treatment group (Prochymal vs placebo) were: peripheral oedema (35.6% vs 33.3%); abdominal pain (22.7% vs 17.23%); thrombocytopenia (22.1% vs 22.2%); hypokalaemia (21.5% vs 13.6%); diarrhoea (22.9% vs 18.5%); hyperglycaemia (20.2% vs 13.6%); and pyrexia (20.2% vs 17.3%).

The TEAEs (first 10 places) occurring more commonly in patients in the Prochymal group than in the placebo group were: (1) confusion and disorientation 11.6% (19.0% vs 7.4%); (2) hypertension 10.4% (17.8% vs 7.4%); (3) confusional state 9.8% (17.2% vs 7.4%); (4) anorexia 8.0% (8.0% vs 0%); (5) anxiety 7.9% (14.1% vs 6.2%), and hypokalaemia 7.9% (21.5% vs 13.6%); (6) hyperkalaemia 7.4% (12.3% vs 4.9%); (7) abdominal distension 7.3% (9.8% vs 2.5%); (8) staphylococcal bacteraemia 6.7% (12.9% vs 6.2%), tremor 6.7% (12.9% vs 6.2%), and insomnia 6.7% (14.1% vs 7.4%); (8) hyperglycaemia 6.6% (20.2% vs 13.6%); (9) mucosal inflammation 6.2% (7.4% vs 1.2%); and (10) dyspnoea 6.1% (18.4% vs 12.3%).

The TEAEs (first 10 places) occurring more commonly in patients in the placebo group than in the Prochymal group were: (1) parainfluenzae virus infection 6.8% (8.6% vs 1.8%); (2) blood alkaline phosphatase increased 6.2% (9.9% vs 3.7%); (3) rectal haemorrhage 5.6% (7.4% vs 1.8%); (4) somnolence 5.5% (8.6% vs 3.1%); (5) hypomagnesaemia 4.9% (7.4% vs 2.5%); (6) ascites 4.4% (9.9% vs 5.5%); (7) gastritis 4.3% (4.9% vs 0.6%) and hypogammaglobulinaemia 4.3% (7.4% vs 3.1%); (8) hyperbilirubinaemia 3.8% (14.8% vs 11.0%); (9) dry mouth 3.7% (11.1% vs 7.4%), upper respiratory infection 3.7% (4.9% vs 1.2%), urinary tract infection bacterial 3.7% (4.9% vs 1.3%), multi organ failure 3.7% (4.9% vs 1.2%), infusion related reaction 3.7% (3.7% vs 0%), and hypoalbuminaemia 3.7% (12.3% vs 8.6%); (10) nausea 3.2% (19.8% vs 16.6%) and hypotension 3.2% (18.9% vs 16.6%).[5]

> **Comment:** All patients in both treatment groups experienced at least 1 TEAE. However, the pattern of TEAEs differed between the two treatment groups. There were four, SOC disorders occurring in at least 10% more patients in the Prochymal group than in the placebo group: Metabolism and Nutrition Disorders; Psychiatric Disorders; Blood and Lymphatic System Disorders; and Cardiac Disorders. However, no SOC disorders were reported in at least 10% more patients in the placebo group than in the Prochymal group.

8.2.2.2. TEAEs by severity

The severity of a TEAE was a qualitative judgment of the degree of intensity, as determined by the Investigator or reported by the patient. The severity of TEAEs was evaluated according to the National Cancer Institute CTCAE grading system (NCI CTCEA Grade): 1=Mild, 2=Moderate, 3=Severe, 4=Life threatening or Disabling, 5=Death related. TEAEs by severity (NCI CTCAE) are summarised in Table 8.

[5] Vomiting: 6.9% (21.0% Placebo versus 14.1% Prochymal); rectal hemorrhage: 5.6% (1.8% Prochymal versus 7.4% Placebo); viral haemorrhagic cystitis 6.2% (1.2% Prochymal versus 7.4% Placebo).

Table 8: Protocol 275 – Overall response (CR + PR) to Prochymal at Day 28; 59 patients

	Prochymal (n=163)	Placebo (n=81)
Grade 1	2 (1.2%)	3 (3.7%)
Grade 2	8 (4.9%)	3 (3.7%)
Grade 3	38 (23.3%)	26 (32.1%)
Grade 4	11 (6.7%)	5 (6.2%)
Grade 5	104 (63.8%)	44 (54.3%)
Grade 3 or higher	153 (93.9%)	75 (92.6%)

Note: (1) At each level of subject summation, subjects reporting more than one TEAE within a primary SOC, HLT, or PT are counted only once at maximum severity. (2) TEAE terms are coded with the MedDRA V11.0 dictionary. (3) Grade (Severity): 1=Mild, 2=Moderate, 3=Severe, 4=Life threatening or Disabling, 5=Death related.

Comment: The majority of TEAEs reported in patients with at least 1 TEAE in both treatment groups were graded 3 or higher (i.e., severe [Grade 3], life threatening or disabling [Grade 4], or death related [Grade 5]).

8.2.2.3. Treatment related adverse events

In the majority of patients, TEAEs were considered unlikely to be related to treatment in both the Prochymal (78.5% [128/163]) and the placebo (81.5% [66/81]) groups. The number of probably related TEAEs were 2 patients (1.2%) in the Prochymal group and 3 patients (3.7%) in the placebo group, and the respective numbers of patients with possibly related TEAEs were 33 (30.2%) and 12 (14.8%). All TEAEs (PT) considered possibly or probably related to treatment occurred in less than 2% of patients in both the Prochymal and placebo groups.

8.2.2.4. TEAEs by subgroup

- **Subjects with at least one TEAEs during second line therapy** (Prochymal vs placebo) with: etanercept (12.3% [20/163] vs 13.6% [11/81]); pentostatin (0% [0/163] vs 4.9% [4/81]); infliximab only (14.1% [23/163] vs 9.9% [8/81]); daclizumab only (6.1% [10/163] vs 7.4% [6/81]; infliximab and daclizumab (3.7% [6/163] vs 6.2% [5/81]); ontak (3.1% [5/163] vs 2.5% [2/81]); campath (0.6% [1/163] vs 0% [0/81]); ATG (12.3% [20/163] vs 12.3% [10/81]); cellcept (17.8% [29/163] vs 19.8% [16/81]); ECP (3.1% [6/163] vs 2.5% [2/81]); and other (9.8% [16/163] vs 4.9% [4/81]). There were no notable differences between TEAEs in patients in the Prochymal and placebo groups regardless of the second-line agent administered. The most frequently administered second line agents were ATG (20%), mycophenolate mofetil (17%), infliximab (16%), etanercept (13%), and daclizumab (11%).
- **TEAEs by type of transplant** (bone marrow, PBSC, or cord blood) occurred in all patients in the groups irrespective of the transplant type. Comparisons between the two treatment groups in TEAEs by transplant type were consistent with the overall comparison between the two treatment groups
- **TEAEs by conditioning regimen** (myeloablative, reduced intensity, or non-myeloablative) occurred in all patients in both treatment groups irrespective of the regimen. In general, the safety profiles of the two treatment groups stratified by conditioning regimen were similar to the safety profiles unstratified by these factors
- **TEAEs by underlying malignancy or leukemic disease** occurred in all patients in both treatment groups irrespective of the underlying disease. In general, the safety profiles of the two treatment groups stratified by underlying malignancy or leukemic disease were similar to the safety profiles unstratified by these conditions

- **TEAEs by age group** (< 18 years; ≥ 18 years) occurred in all patients in both treatment groups. However, the safety data in patients aged < 18 years should be interpreted cautiously due to the small number of subjects in this age group in the safety population (Prochymal n=14; placebo n=13). In patients aged < 18 years, disorders (SOC) with ≥ 10% more patients in the Prochymal group than in the placebo group were: gastrointestinal absolute difference of 18.1% (64.3%, n=9 vs 46.2%, n=6), compared with -8.6% in patients aged ≥ 18 years; psychiatric absolute difference of 14.3% (14.3%, n=2 vs 0%), compared with 14.3% in patients aged ≥ 18 years; renal and urinary absolute difference of 13.7% (21.4%, n=3 vs 7.7%, n=1), compared with -5.5% in patients aged ≥ 18 years; skin and subcutaneous tissues absolute difference of 20.3% (35.7%, n=5 vs 15.4%, n=2), compared with 4.6% in patients aged ≥ 18 years; endocrine absolute difference of 13.7% (21.4%, n=3 vs 7.2%, n=1), compared with -0.4% in patients aged ≥ 18 years
- **TEAEs by donor compatibility** (related or unrelated) occurred in all patients in both treatment groups. The most notable differences in the safety profiles based on SOC disorders (i.e., ≥ 10% absolute difference [Prochymal minus placebo] in the unrelated vs related groups) were: blood and lymphatic system (6.8% unrelated vs 16.2% related); eye (-5.0% unrelated vs 9.6% related); metabolism and nutrition (11.3% unrelated vs 30.2% related); musculoskeletal and connective tissue (2.6% unrelated vs -8.6% related); nervous system (-0.4% unrelated vs -14.5% related); respiratory, thoracic and mediastinal (-1.5% unrelated vs 8.3% related); skin and subcutaneous system (14.3% unrelated vs 1.2% related); vascular (19.0% unrelated vs -15.5% related). Overall, there was no evidence that the safety profile of Prochymal in patients with unrelated donor compatibility was notably worse than the safety profile in patients with related donor compatibility
- **TEAEs by baseline grade of acute GVHD (B, C, D)** occurred in all patients in both treatment groups. There were no significant differences across the three grades in the proportion of patients experiencing SOC disorders in either the Prochymal or placebo group (i.e., higher baseline grades of acute GVHD were not associated with higher risks of TEAEs). In general, the safety profiles of the two treatment groups stratified by baseline acute GVHD grade were similar to the safety profiles unstratified by these factors.

8.2.2.5. Deaths and other serious adverse events

Deaths

In the safety population, 64.4% (105/163) of patients in the Prochymal group died due to a serious adverse event compared with 54.3% (44/81) of patients in the placebo group. In both treatment groups, death was primarily due to 'infections and infestations' (Prochymal 25.8%, n=42 and placebo 14.8%, n=12). The only other SOC disorder resulting in ≥ 10% of deaths in at least one of the treatment groups was 'immune system disorders' (Prochymal 14.1%, n=23 and placebo 6.2%, n=5). The most common SAEs (PT) leading to death and occurring in ≥ 2% of patients in at least one of the two treatment groups (Prochymal vs placebo) were: GVHD (9.8%, n=16 vs 4.9%, n=4); sepsis (4.9%, n=8 vs 4.9%, n=4); respiratory failure (3.7%, n=6 vs 1.2%, n=1.2%); acute myeloid leukemia (3.1%, n=5 vs 2.5%, n=2); pneumonia (2.5%, n=4 vs 2.5%, n=2); gastrointestinal haemorrhage (1.8%, n=3 vs 2.5%, n=2); multi-organ failure (1.8%, n=3 vs 6.2%, n=5); intracranial haemorrhage (1.2%, n=1 vs 2.5%, n=2); cardio-respiratory arrest (0.6%, n=1 vs 3.7%, n=3); enterococcal sepsis (0.6%, n=1 vs 2.5%, n=2); and hepatorenal failure (0% vs 2.5%, n=2). The Grade of acute GVHD at baseline correlated with death (Table 9). Subjects were considered dead if survival status at Day 180 was unknown.

Table 9: Protocol 280 – Survival status at 180 days; mITT population

	GVHD Grade B		GVHD Grade C		GVHD Grade D	
Outcome	Prochymal, n=37	Placebo, n=21	Prochymal, n=82	Placebo, n=46	Prochymal, n=44	Placebo, n=14
Survival > 180 days	18 (48.6%)	10 (47.6%)	26 (31.7%)	20 (43.5%)	12 (27.3%)	4 (28.6%)
Survival ≤ 180 days	19 (51.4%)	11 (52.4%)	56 (68.3%)	26 (56.5%)	32 (72.7%)	10 (71.4%)
Confirmed ≤ 180 days	17 (45.9%)	10 (47.6%)	53 (64.6%)	23 (50.0%)	30 (68.2%)	8 (57.1%)
Censored ≤ 180 days	2 (5.4%)	1 (4.8%)	3 (3.7%)	3 (6.5%)	2 (4.5%)	2 (14.3%)

Overall, 42 of the 58 (74%) patients with Grade D GVHD did not survive ≥ 180 days (32 of 44 Prochymal [72.7%] and 10 of 14 placebo patients [71.4%]). The cause of death differed by Grade of GVHD, with the incidence of death due to 'infections and infestations' being highest for Grade D patients. Overall, 25 of the 42 (60%) of the Grade D patients died from an 'infection or infestation' compared with 29 of 112 (26%) of the Grade B/C patients. The proportion of patients with GVHD Grade D disease with death due to 'infections and infestations' was higher in the Prochymal group (25.8%, n=44) than in the placebo group (14.8%, n=14).

In the placebo group, all patient deaths were considered to be unlikely to be related to study medication. In the Prochymal group, 102 of the 105 deaths (97.1%) were considered to be unlikely to be related to study medication, 3 (3%) were considered possibly related, and 0 were deemed probably related. The 3 patients whose deaths were considered possibly related to Prochymal died due to veno-occlusive liver disease (1 patient), adenoviral hepatitis (1 patient), and bacteremia (1 patient).

Other serious adverse events (SAEs)

SAEs included any AE that resulted in death, was life-threatening, resulted in persistent or significant disability or incapacity, required inpatient hospitalisation or prolonged hospitalisation, resulted in a congenital anomaly or birth defect, or was a medically significant event that required medical or surgical intervention.

The percentage of patients who experienced at least 1 SAE was 89.5% (n=146) in the Prochymal group and 87.7% (n=71) in the placebo group. The most commonly reported SAEs (PT), occurring in ≥ 5% of patients in either treatment group (Prochymal vs placebo) listed by decreasing frequency in the Prochymal group were: GvHD (14.7%, n=24 vs 11.1%, n=9); gastrointestinal haemorrhage (7.4%, n=12 vs 6.2%, n=5); sepsis (8.6%, n=14 vs 7.4%, n=6); GVHD in intestine (6.7%, n=11 vs 3.7%, n=3); pneumonia (6.1%, n=10 vs 3.7%, n=3); respiratory failure (6.1%, n=10 vs 6.2%, n=5); bacteraemia (5.5%, n=9 vs 3.7%, n=3), and multi-organ failure (2.5%, n=4 vs 7.4%, n=6).

SAEs (PT) occurring in ≥ 2% and < 5% of patients in the Prochymal group, and with equal or greater frequency compared with the placebo group were: pyrexia (3.7%, n=6 vs 3.7%, n=3); adenovirus infection (3.1%, n=5 vs 1.2%, n=1); acute myeloid leukemia (3.1%, n=5 vs 2.5%, n=2); renal failure (3.1%, n=5 vs 2.5%, n=2); atrial fibrillation (2.5%, n=4 vs 1.2%, n=1); septic shock (2.5%, n=4 vs 2.5%, n=2); cytomegalovirus infection (2.5%, n=4 vs 2.5%, n=2); staphylococcal bacteraemia (2.5%, n=4 vs 1.2%, n=1); klebsiella bacteraemia (2.5%, n=4 vs 1.2%, n=2); renal failure acute (2.5%, n=4 vs 2.5%, n=2); and respiratory distress (2.5%, n=2 vs 1.2%, n=1);

SAEs (PT) occurring in ≥ 2% and < 5% of patients in the placebo group, and more frequently than in the Prochymal group were (Prochymal vs placebo): diarrhoea (1.8%, n=3 vs 2.5%, n=2); convulsion (1.8%, n=3 vs 2.5%, n=2); acute respiratory distress syndrome (1.8%, n=3 vs 2.5%, n=2); hypotension (1.8%, n=3 vs 2.5%, n=2); thrombocytopenia (1.2%, n=2 vs 2.5%, n=2); acute cholecystitis (1.2%, n=2 vs 2.5%, n=2); hyperbilirubinaemia (1.2%, n=2 vs 3.7%, n=2); staphylococcal sepsis (1.2%, n=2 vs 2.5%, n=2); intracranial haemorrhage (1.2%, n=2 vs 2.5%, n=2); acute respiratory failure (1.2%, n=2 vs 3.7%, n=3); hypoxia (1.2%, n=1 vs 2.5%, n=2); enterococcal sepsis (0.6%, n=1 vs 3.7%, n=3); viral haemorrhagic cystitis (0.6%, n=1 vs 6.2%, n=5); pancytopenia (0.6%, n=1 vs 2.5%, n=2); cardio-respiratory arrest (0.6%, n=1 vs 3.7%,

n=3); staphylococcal infection (0.6%, n=1 vs 2.5%, n=2); clostridium difficile colitis (0.6%, n=1 vs 2.5%, n=2); neutropenia (0%, n=0 vs 2.5%, n=2); ileus (0%, n=0 vs 2.5%, n=2); hepatorenal failure (0%, n=0 vs 2.5%, n=2); pneumonia staphylococcal (0%, n=1 vs 2.5%, n=2); enterococcal infection (0%, n=0 vs 2.5%, n=2); and pneumonia viral (0%, n=0 vs 3.7%, n=3).

SAEs considered to be directly related to steroids were reported in 6 patients: Prochymal 5 (pancreatitis, steroid myopathy, disorientation, mood altered, mental state changes); and placebo 1 (mental state changes).

The overall proportion of patients with at least 1 SAE by severity (NCI-CTCAE grade) in the two treatment groups is summarised below in Table 10.

Table 10: Protocol 280 – Proportion of patients with at least 1 SAE by severity; safety population

	Prochymal (n=163)	Placebo (n=81)
Grade 1	1 (0.6%)	0 (0.0%)
Grade 2	4 (2.5%)	3 (3.7%)
Grade 3	29 (17.8%)	22 (27.2%)
Grade 4	8 (4.9%)	2 (2.5%)
Grade 5	104 (63.8%)	44 (54.3%)

Note: At each level of subject summation, subjects reporting more than one serious adverse event within a primary system organ class, high level term, or preferred term are counted only once at maximum severity.
Note: Adverse event terms are coded with the MedDRA V11.0 dictionary.
Note: Grade (Severity): 1=Mild, 2=Moderate, 3=Severe, 4=Life threatening or Disabling, 5=Death related.

8.2.2.6. Discontinuations due to adverse events

At least 1 TEAE resulting in permanent discontinuation was reported in 9.2% (15/163) of patients in the Prochymal group and 13.6% (11/81) of patients in the placebo group. There were a total of 30 TEAEs reported as leading to discontinuation in one or both of the two treatment groups. The only TEAE reported as leading to discontinuation in more than 1 patient in either of the two treatment groups was hypoxia (3 patients in the Prochymal group).

8.2.2.7. TEAEs and SAEs related to infusional toxicity

Infusional toxicity was evaluated at each infusion by continuously monitoring vital signs and SaO2/SAT (via pulse oximetry) from the time of Investigational Agent administration until 2 hours after starting the infusion. TEAEs and SAEs related to infusional toxicity were reported in 1.8% (n=3) of patients in the Procyhmal group and 2.5% (n=2) of patients in the placebo group. The 3 events in the Prochymal group all occurred > 24 hour after the infusion and were: pericarditis (SAE); generalised oedema (SAE); and blood bicarbonate decreased (not serious). The 2 events (not serious) in the placebo groups of erythema and hypotension both occurred within 24 hours of the infusion. No infusions were interrupted due to infusional toxicity, AEs, SaO2 decrease, infusion bag expired, or withdrawal of patient consent. TEAEs occurring within 24 hours of the infusion, but considered not related to infusional toxicity, were reported in 49.1% (n=80) of patients in the Prochymal group and 39.5% (n=32) of patients in the placebo group. The major difference between the two treatment groups was the higher incidence of 'investigation' (SOC) disorders in the Prochymal group (9.2%, n=15) compared with the placebo group 1.2% (n=1).

8.2.2.8. TEAEs related to ectopic tissue formation

In order to investigate possible ectopic tissue formation (assessed at study sites), computed tomography (CT) scan or magnetic resonance imaging (MRI) of chest, abdomen, and pelvis was conducted at screening and following treatment at the Day 180/End-of-study assessment. There were no TEAEs related to ectopic tissue formations in either of the two treatment groups.

Ectopic tissue formations not categorised as TEAEs were reported at screening in 6 patients in the Prochymal group (2 x chest; 3 x abdomen; 1 x pelvis), and no patients in the placebo group. At Day 180/End-of-Study assessment, ectopic tissue formations not categorised as TEAEs were reported in 1 patient in the Prochymal group (1 x chest), and 2 patients in the placebo group (1x chest; 1 x abdomen). Change from screening to Day 180/End-of-Study assessment in ectopic tissue formations were reported in 1 patient in the Prochymal group (1 x chest) and 2 patients in the placebo group (1 x chest; 1 x abdomen).

8.2.2.9. TEAEs by relapse of underlying disease

A patient was considered relapsed (by the Investigator) when there was a recurrence of the underlying malignancy or leukemic disease after transplantation. If a patient had multiple TEAEs associated with relapse of underlying malignancy or leukemic disease, the patient was only counted once. Relapse was assessed at Day 180/End-of-study. Overall, there was no notable difference between the two treatment groups in the proportion of patients with at least 1 TEAE indicating relapse of underlying disease (Prochymal 8.0%, n=13; placebo 9.9%, n=8).`The most commonly occurring TEAE indicating relapse of underlying disease in both treatment groups was acute myeloid leukaemia (Prochymal 3.7%, n=6; placebo 2.5%, n=2). The only other TEAE indicating relapse of disease and occurring in ≥ 2 patients was leukemia in the Prochymal group.

8.2.3. Laboratory tests

8.2.3.1. Data

Clinical chemistry, haematology, and coagulation laboratory data were summarised using shift tables by treatment group. Observed results were compared with the normal range and considered to be within the normal range, high value compared with the upper limit of the range, or low value compared with the lower limit of the range. Shift tables compared results with the baseline value for the scheduled visits. The parameters were assessed at Screening, Week 1 through to Week 9 (inclusive), and then at Day 100, 130, 160 and 180. There was an increase in the number of missing patient data for all clinical laboratory test parameters over the course of the study.

8.2.3.2. Liver function

There were no marked shifts from baseline over time in standard liver function test results in either the Prochymal or placebo treatment groups, and there were no marked differences between the two treatment groups at any time points.

8.2.3.3. Kidney function

There were no marked shifts from baseline over time in BUN or serum creatinine levels in either the Prochymal or placebo treatment groups, and there were no marked differences between the two treatment groups at any time points.

8.2.3.4. Other clinical chemistry

There were no marked shifts from baseline over time in other standard clinical chemistry results in either the Prochymal or placebo treatment groups, and there were no marked differences between the two treatment groups at any time points.

8.2.3.5. Haematology

There were no marked shifts from baseline over time the standard range of haematological test results (including coagulation) in either the Prochymal or placebo treatment groups, and there were no marked differences between the two treatment groups at any time points.

8.2.3.6. Other safety parameters

Vital signs

There were no marked shifts from baseline over time in heart rate, respiratory rate, or oxygen saturation in the two treatment groups, and there were no marked differences in these parameters between the two treatment groups at any time points. There was a reduction in mean systolic blood pressure, mean diastolic blood pressure and mean weight over the course of the study in both treatment groups, but the reductions were not markedly different between the two treatment groups.

Electrocardiogram

There were no marked changes in 12-lead ECG parameters (including QTc intervals) from baseline to Day 180/End-of-study assessment in the two treatment groups, and there were no marked differences between the two treatment groups at either of these two time-points.

8.3. Protocol 275

8.3.1. Patient exposure

Protocol 275 included a total of 59 paediatric and adolescent patients aged < 18 years. The mean ± SD total number of Prochymal infusions received was 9.8 ± 4.0 (range: 2, 20). Of the 59 patients, 26 (44.1%) received ≤ 8 infusions and 33 (55.9%) received > 8 infusions. The mean ± SD duration of Prochymal exposure was 41.7 ± 25.4 days (range: 3, 116 days).

8.3.2. Adverse events

Only SAEs were collected in Protocol 275.

8.3.3. Deaths and other serious adverse events

8.3.3.1. Deaths

There were 22 (37.3%) patients with at least 1 SAE leading to death. The most commonly reported SAE leading to death was respiratory failure (4 [6.8%] patients). The next most commonly reported SAEs leading to death (each reported in 2 patients) were multi-organ failure, GVHD, and mucormycosis. Only one SAE leading to death was considered to be treatment related (pulmonary haemorrhage).

8.3.3.2. Other SAEs

There were 35 (59.3%) patients with at least 1 SAE (total number of events = 74). Of these 35 patients, SAEs leading to death were reported in 22 and SAEs not leading to death were reported in 13 (Grade 2 [4 patients], Grade 3 [4 patients], Grade 4 [5 patients]).The most commonly reported SAEs (SOC) were 'infections and infestations' (15 [25.4%] patients), followed by 'respiratory, thoracic and mediastinal disorders' (11 [18.6%] patients), 'gastrointestinal disorders' (7 [11.9%] patients), and 'general disorders and administration site conditions' (6 [10.2%] patients). All other SAEs (SOC) were reported in ≤ 3 patients. The most frequently reported SAEs (PT) were respiratory failure (6 [10.2%] patients) and multi-organ failure (4 [6.8%] patients). No other SAEs were reported in more than 2 patients. Of the 35 patients with at least 1 SAE, 4 events in 4 patients were reported as possibly related to treatment (neutropenia, infusion-related, pulmonary hemorrhage, and hypertension).

8.3.4. Discontinuations due to SAEs

One patient experienced an infusion reaction (SAE) leading to treatment discontinuation and considered by the Investigator to be possibly related to Prochymal. This SAE followed the second infusion and was characterised by an increase in body temperature, decrease in blood pressure, and tachypnoea occurring 2 hours after completion of the infusion and resolving

within 2 hours. This patient had also experienced a similar infusion reaction following the first infusion.

8.3.5. Clinical laboratory tests

Laboratory parameters including complete blood count (CBC) with differential, PT, PTT, chemistry and urinalysis were assessed. However, these data were not collected in Protocol 275, but abnormalities in laboratory parameters assessed by the Investigator as meeting the criteria for SAEs were reported. These laboratory test SAEs included: abnormal blood electrolytes and hypochloraemic alkalosis in 1 patient; neutropenia considered possibly related to Prochymal and leading to treatment discontinuation in 1 patient; and renal failure in 2 patients.

8.3.6. Other safety parameters

8.3.6.1. Vital signs

Prior to, during, and after each infusion of Prochymal, BP, HR, respiratory rate, temperature, and SaO2/SAT were monitored. No abnormal values were recorded for any patient during the monitoring period. Hypertension (SAE) was reported in 2 patients.

8.3.6.2. Electrocardiographic (ECG)

ECGs were to be performed for each patient prior to treatment (screening) and at the Day 100 visit. Of the patients who survived to Day 100 and had an ECG, no significant findings were reported. There were 7 patients with an end-of-study visit ECG finding that was not present at baseline: 2 x right atrial enlargement; 1 x possible right atrial enlargement; 1 x sinus bradycardia, right atrial enlargement, possible right ventricular hypertrophy; 1 x sinus tachycardia, regular sinus rhythm in V1 or V2, probably normal variant versus incomplete right bundle branch block; 1 x sinus rhythm with 1st degree AV block, left axis deviation, nonspecific intraventricular block; and 1 x sinus tachycardia. None of these findings were reported as SAEs.

> **Comment:** Of the 7 patients with an end-of-study ECG abnormality not present at baseline, 3 were reported as having right atrial enlargement and 1 was reported as having possible right atrial enlargement. Of the 2 patients reported with right atrial enlargement, 1 had a history of pneumonitis and cytomegalovirus infection and 1 had a history of sleep apnoea and experienced aspiration pneumonia during the study, and the 1 patient with possible right atrial enlargement had a history of cytomegalovirus infection. It is postulated in the CSR that the medical conditions reported in these 3 patients might have contributed to the development of right atrial enlargement.

8.3.6.3. Infusional toxicity

Infusional toxicity was evaluated by monitoring vital signs (HR, respiration rate, temperature, and BP) and SaO2/SAT from 30 minutes prior to infusion through 2 hours post infusion. No abnormal observations were recorded in association with Prochymal infusion for any patient. However, as mentioned above, 1 patient had 2 infusion reactions indentified by the Investigator as a SAE. Out of 581 infusions administered, there were only 2 reports of an infusion being interrupted.

8.3.6.4. Ectopic tissue formation

CT scans (head, chest, and abdomen) were to be performed for each patient prior to the first infusion and at the Day 100 visit. No CT findings indicating ectopic tissue formation were reported in those patients with CT scan data at Day 100. In addition, no SAEs were reported as possibly representing ectopic tissue foci.

8.3.6.5. Relapse of underlying malignancy or leukemic disease

Relapse was determined by recurrence of the underlying malignancy or leukemic disease for which the HSCT had been performed. Relapse of the underlying disease was reported as a SAE

in 2 (3.4%) patients: 1 with acute lymphocytic leukemia and 1 with acute myeloid leukemia. In both of these patients relapse of the underlying disease resulted in death.

8.4. Safety issues with the potential for major regulatory impact

8.4.1. Liver toxicity

8.4.1.1. Protocol 280

In Protocol 280, the proportion of patients reported as experiencing at least 1 TEAE classified as 'hepatobiliary disorders' (SOC) was 25.8% (n=42) in the Prochymal group and 27.2% (n=22) in the placebo group. The only reported HLT occurring in ≥ 10% of patients in at least one of the two treatment groups was 'cholestasis and jaundice' (Prochymal 16.6%; placebo 18.5%). The only TEAE (PT) reported as occurring in ≥ 5% of patients in the Prochymal group and ≥ 2% more commonly than in the placebo group was jaundice (6.1% vs 3.7%).

SAEs 'hepatobiliary disorders' (SOC) leading to death were reported in 2 (1.2%) patients in the Prochymal group and 3 (3.7%) patients in the placebo group. The SAEs (PT) leading to death were hepatic failure (x1) and veno-occlusive disease (x1) in the Prochymal group, and hepatorenal failure (x2) and hepatic failure (x1) in the placebo group. SAEs (all) 'hepatobiliary disorders' (SOC) were reported in 8.0% of patients in the Prochymal group and 13.6% of patients in the placebo group. There were no SAEs (PT) (including events leading to death) reported as occurring in ≥ 2% of patients in the Prochymal group and ≥ 1% more commonly than in the placebo group.

There were no notable changes in standard clinical chemistry LFT levels during the course of Protocol 280 in either the Prochymal or placebo groups, or between the two treatment groups at the various scheduled time point assessments.

8.4.2. Haematological toxicity

8.4.2.1. Protocol 280

In Protocol 280, the proportion of patients reported as experiencing at least 1 TEAE classified as 'blood and lymphatic tissue disorders' (SOC) was 45.4% (n=74) in the Prochymal group and 34.6% (n=28) in the placebo group. The reported HLTs occurring in ≥ 10% of patients in at least one of the two treatment groups (Prochymal vs placebo) were 'thrombocytopenia' (24.5% vs 22.2%), anaemias NEC' (14.7% vs 14.8%) and 'neutropenias' (14.1% vs 9.9%). TEAEs (PT) reported as occurring in ≥ 5% of patients in the Prochymal group and ≥ 2% more commonly than in the placebo group were neutropenia (11.7% vs 7.4%) and pancytopenia (6.1% vs 4.9%).

SAEs 'blood and lymphatic tissue disorders' (SOC) leading to death were reported in 1 (0.6%) patient in the Prochymal group and 1 (1.2%) patient in the placebo group. The SAEs (PT) leading to death were thrombotic thrombocytopenic purpura (x1) in the Prochymal group and thrombotic microangiopathy (x1) in the placebo group. SAEs (all) 'blood and lymphatic tissue disorders' (SOC) were reported in 6.7% of patients in the Prochymal group and 6.2% of patients in the placebo group. There were no SAEs (PT) reported as occurring in ≥ 2% of patients in the Prochymal group and ≥ 1% more commonly than in the placebo group.

There were no notable changes in standard laboratory test haematological parameters during the course of Protocol 280 in either the Prochymal or placebo groups, or between the two treatment groups at the various scheduled time point assessments.

8.4.3. Renal toxicity

8.4.3.1. Protocol 280

In Protocol 280, the inclusion criteria included patients with adequate renal function (creatinine clearance of > 30 mL/min in adults as defined by the Cockcroft-Gault equation), and by the Schwartz equation in paediatric patients based on age.

The proportion of patients reported as experiencing at least 1 TEAE classified as 'renal and urinary disorders' (SOC) was 39.9% (n=65) in the Prochymal group and 40.7% (n=33) in the placebo group. The reported HLTs occurring in ≥ 10% of patients in at least one of the two treatment groups (Prochymal vs placebo) were 'renal failure and impairment' (21.5%, n=35 vs placebo 21.0%, n=17) and 'bladder and urethral symptoms' (16.6%, n=27 vs 17.3%, n=14). The only TEAE (PT) reported as occurring in ≥ 5% of patients in the Prochymal group and ≥ 2% more commonly than in the placebo group was renal failure acute (9.2% vs 6.2%).

SAEs 'renal and urinary disorders' (SOC) leading to death were reported in 1 (0.6%) patient in the Prochymal group and no (0%) patients in the placebo group. The SAE (PT) leading to death in the Prochymal group was renal failure (x1). SAEs (all) 'renal and urinary disorders' (SOC) were reported in 7.4% of patients in the Prochymal group and 9.9% of patients in the placebo group. There were no SAEs (PT) reported as occurring in ≥ 2% of patients in the Prochymal group and ≥ 1% more commonly than in the placebo group.

There were no notable changes in BUN or serum creatinine levels during the course of Protocol 180 in either the Prochymal or placebo groups, or between the two treatment groups at the various scheduled time point assessments.

8.4.4. Serious skin reactions

8.4.4.1. Protocol 280

In Protocol 280, the proportion of patients reported as experiencing at least 1 TEAE classified as 'skin and subcutaneous tissue disorders' (SOC) was 43.6% (n=71) in the Prochymal group and 35.8%% (n=29) in the placebo group. The reported HLTs occurring in ≥ 10% of patients in at least one of the two treatment groups (Prochymal vs placebo) were 'dermal and epidermal conditions NEC' (13.5% and 7.4%), and 'rashes, eruptions, and exanthems NEC' (13.5% vs 7.4%). TEAEs (PT) reported as occurring in ≥ 5% of patients in the Prochymal group and ≥ 2% more commonly than in the placebo group were rash (11.7% vs 6.2%), and decubitus ulcer (5.5% vs 1.2%).

There were no SAEs 'skin and subcutaneous tissue disorders' (SOC) leading to death. SAEs (all) 'skin and subcutaneous tissue disorders' (SOC) were reported in 1.2% of patients in the Prochymal group and 1.2% of patients in the placebo group. There were no SAEs (PT) reported as occurring in ≥ 2% of patients in the Prochymal group and ≥ 1% more commonly than in the placebo group.

8.4.5. Cardiovascular safety

8.4.5.1. Protocol 280

Cardiac disorders

In Protocol 280, the proportion of patients reported as experiencing at least 1 TEAE classified as 'cardiac disorders' (SOC) was 34.4% (n=56) in the Prochymal group and 23.5% (n=19) in the placebo group. The reported HLTs occurring in ≥ 10% of patients in at least one of the two treatment groups (Prochymal vs placebo) were 'rate and rhythm disorder disorders NEC' (16.0%, vs 11.1%) and 'supraventricular arrhythmias' (12.9% vs 6.2%). TEAEs (PT) reported as occurring in ≥ 5% of patients in the Prochymal group and ≥ 2% more commonly than in the placebo group were: tachycardia (14.1% vs 9.9%) and atrial fibrillation (8.6% vs 3.7%).

SAEs 'cardiac disorders' (SOC) leading to death were reported in 2 (1.2%) patients in the Prochymal group and 4 (4.9%) patients in the placebo group. The SAEs (PT) leading to death in the Prochymal group were cardiac tamponade (x1) and cardio-respiratory arrest (1x), and in the placebo group were cardio-respiratory arrest (x3) and cardiopulmonary failure (x1). SAEs (all) 'cardiac disorders' (SOC) were reported in 5.5% of patients in the Prochymal group and 8.6% of patients in the placebo group. The only SAE (PT) reported as occurring in ≥ 2% of

patients in the Prochymal group and ≥ 1% more commonly than in the placebo group was atrial fibrillation (2.5% vs 1.2%).

Vascular disorders

In Protocol 280, the proportion of patients experiencing at least 1 TEAE classified as 'vascular disorders' (SOC) was 36.8% (n=60) in the Prochymal group and 38.3% (n=31) in the placebo group. The reported HLTs occurring in ≥ 10% of patients in at least one of the two treatment groups (Prochymal vs placebo) were 'vascular hypertensive disorders NEC' (17.8% vs 7.4%) and 'vascular hypotensive disorders' (17.2% vs 22.2%). The only TEAE (PT) reported as occurring in ≥ 5% of patients in the Prochymal group and ≥ 2% more commonly than in the placebo group was hypertension (17.8% vs 7.4%).

There were no SAEs 'vascular disorders' (SOC) leading to death. SAEs (all) 'vascular disorders' (SOC) were reported in 2.5% of patients in the Prochymal group and 3.7% of patients in the placebo group. There were no SAEs (PT) reported as occurring in ≥ 2% of patients in the Prochymal group and ≥ 1% more commonly than in the placebo group.

8.4.5.2. Protocol 401 – Acute myocardial infarction (6-month follow-up)

The submitted data included a synopsis of a Phase 1, randomised, double-blind, placebo-controlled, dose-escalation, multi-centre study to determine the safety of Prochymal following acute myocardial infarction (Protocol 401). The study included data from 13 participating sites in the USA and was undertaken from 22 March 2005 to 4 October 2006. The study included adult patients (male and female) who had experienced a first myocardial infarction 1 to 10 days prior to randomisation. Subjects must have had a patent infarct related artery demonstrated by coronary arteriogram, and global left ventricular systolic dysfunction with an ejection fraction of ≤ 60% and ≥ 30%.

The study randomised patients (2:1 ratio) to Prochymal or placebo into one of 4 cohorts. A total of 60 subjects in 4 cohorts were enrolled, out of which 53 subjects were treated at 10 sites. Blinded study treatment was infused intravenously for total doses of 0.5, 1.6, and 5 × 10^6 hMSCs/kg for Cohorts 1, 2, and 3, respectively, and Cohort 4 also received the highest dose of 5 × 10^6 hMSCs/kg. The infusion was given once over a period ranging from 7 minutes to 137 minutes, depending on dose cohort and body weight of the subject. If the lower doses of Prochymal were well tolerated, subsequent dose cohorts and 1 additional safety cohort at the highest tolerated dose were to be enrolled, with a target enrolment of 48 subjects. Subjects were followed for 6 months.

The primary safety endpoint was TEAE rates between Prochymal (0.5, 1.6, and 5.0 x 10^6 hMSC/kg) and placebo. Safety measures included reported/observed AEs, vital signs, physical examination, 12-lead electrocardiogram (ECG), 24-hour Holter ECG recording, 16-segment echocardiogram, Karnofsky performance status score, laboratory safety tests, infection assessment, pulse oximetry, major adverse cardiac events endpoints, and computed tomography scan of the chest, abdomen, and pelvis.

The submitted data included a summary of the change from baseline in pulmonary function tests (FEV1) over the first 7 days and then at months 1, 2, 3 and 6, and oxygen saturation (pulse oximetry) over the first 6 hours following the infusion. No significant differences were observed between Prochymal and placebo, but there were no comparative statistical analyses between treatment groups. No other numerical results for the safety endpoints were provided. The synopsis concluded that – 'Prochymal was well-tolerated at each dose level studied. There were no differences between proportions of Prochymal and placebo subjects with AEs in each system organ class. Significantly fewer Prochymal subjects than placebo subjects experienced arrhythmias... Treatment with Prochymal was shown to be safe at the dose levels studied.'

> **Comment:** The submission included only a synopsis of Protocol 401 results. The full study report was not requested. Limited safety data from this protocol was included

with the synopsis. In this protocol, subjects were followed-up for 6 months after receiving a single iv dose of Prochymal (0.5, 1.6, and 5.0 x 10^6 hMSC/kg) or placebo. Patient numbers in the treatment cohorts were: Cohort 1 (Prochymal 0.5 x 10^6 hMSC/kg [n=9] vs placebo [n=5]); Cohort 2 (Prochymal 1.6 x 10^6 hMSC/kg [n=10] vs placebo [n=4]); and Cohort 3 & 4 (Prochymal 5.0 x 10^6 hMSC/kg [n=15] vs placebo [n=10]). Lung function tests (FEV1) were assessed at regular intervals for 6-months and there were no marked differences among the three Prochymal dose cohorts or between Prochymal and placebo. Similarly, there were no marked differences in post-infusion pulse oximetry results among the Prochymal dose cohorts, or between Prochymal and placebo.

8.4.5.3. Protocol 402 – Acute myocardial infarction (2 year follow-up)

The submitted data included a synopsis of a Phase I, multi-centre, long-term, follow-up study to evaluate the safety of Prochymal in subjects following acute myocardial infarction (Protocol 402). The objective of this study was to establish the long-term safety of single-dose Prochymal compared with placebo in subjects from Protocol 401 who had been treated after an acute myocardial infarction. The study was undertaken from 29 September 2005 to 24 April 2008. In Protocol 401, patients were followed for 6 months, while in Protocol 402 patients were followed for an additional 1.5 years resulting in a total follow-up of 2 years. Only subjects who completed Protocol 401 were eligible for enrolment in the safety extension study, and of the 53 subjects who completed Protocol 401 there were 52 subjects who were subsequently enrolled into Protocol 402.

The safety endpoints included: (1) serious adverse event (SAE) rates among patients who received 0.5, 1.6, or 5.0 × 10^6 hMSCs/kg Prochymal or placebo in Protocol 401; and (2) survival rates among patients who received 0.5, 1.6, or 5.0 × 10^6 hMSCs/kg Prochymal or placebo in Protocol 401. Safety measures included monitoring and recording of all adverse events (AEs), subject survival status, vital signs, physical examinations, 12-lead electrocardiogram, Karnofsky performance status score, major adverse cardiac event endpoints, and computed tomography scans of the chest, abdomen, and pelvis. The study also included a number of exploratory efficacy endpoints.

Only a synopsis of the safety results was provided. The study synopsis included the following summary of the safety results – 'There were a total of 11 SAEs reported for 9 of 33 subjects (27.3%) in the Prochymal group and 8 SAEs reported for 7 of 19 subjects (36.8%) in the placebo group. The survival rate was 100% for both groups. For all cohorts, more subjects in the placebo group (12 of 19; 63.2%) than in the Prochymal group (8 of 33; 24.2%) had AEs in the general disorders and administration site conditions system organ class (P=0.008). In the placebo group, 42.1% (8 of 19) of subjects experienced AEs in the respiratory, thoracic, and mediastinal disorders system organ class compared with 15.2% (5 of 33) of subjects in the Prochymal group (all cohorts) (P=0.047). There were no AEs reported as probably related to study treatment and similar proportions of subjects in the Prochymal and placebo groups experienced AEs reported as possibly related to study treatment. The proportions of subjects with AEs representing ectopic tissue formation and cardiac disorders were similar between the treatment groups. No important changes were observed in vital signs, physical examinations, ECGs, Karnofsky performance status scores, major adverse cardiac event endpoints, or computed tomography scans. There were no significant trends observed in the safety data during this study'.

Comment: The submission included only a synopsis of Protocol 402 results. The full study report was not requested. Based on the limited summary of the 2-year safety data provided in the synopsis of Protocol 402, there appears to be no notable difference in the safety profile of single-dose Prochymal and placebo over the 2 years following acute myocardial infarction. However, these data are of limited relevance given that at least 8 Prochymal infusions over a 4 week period are proposed for approval (i.e. 2 infusions per week for 4 consecutive weeks).

8.4.6. Unwanted immunological events

8.4.6.1. Protocol 280

In Protocol 280, the proportion of patients reported as experiencing at least 1 TEAE classified as 'immune system disorders' (SOC) was 36.2% (n=59) in the Prochymal group and 30.9% (n=25) in the placebo group. The only HLT occurring in ≥ 10% of patients in either of the two treatment groups (Prochymal vs placebo) was 'transplant rejections' (35.0% vs 25.9%). TEAEs (PT) reported as occurring in ≥ 5% of patients in the Prochymal group and ≥ 2% more commonly than in the placebo group were GVHD (19.6% vs 14.8%) and acute GHVD in intestine (8.6% vs 3.7%).

SAEs 'immune system disorders' (SOC) were the second most common group of disorders in both treatment groups leading to death after 'infections and infestations'. SAEs 'immune system disorders' (SOC) leading to death were reported in 42 (25.8%) patients in the Prochymal group and 12 (14.8%) patients in the placebo group. The SAEs (PT) leading to death in the Prochymal vs placebo group were GVHD (9.8% vs 4.9%), acute GVHD in intestine (1.8% vs 1.2%), acute GVHD (1.2% vs 0%), and acute GVHD in liver (1.2% vs 0%). SAEs (all) 'immune system disorders' (PT) were reported in 23.9% of patients in the Prochymal group and 17.3% of patients in the placebo group. SAEs (PT) reported as occurring in ≥ 2% of patients in the Prochymal group and ≥ 1% more commonly than in the placebo group were GVHD (14.7% vs 11.1%) and acute GVHD in intestine (6.7% vs 3.7%).

8.5. Other safety issues

8.5.1. Specifically related to this application

8.5.1.1. Metabolism and nutrition

In Protocol 280, 'metabolism and nutrition disorders' (SOC) occurred notably more commonly in patients in the Prochymal group (67.5%, [n=110], 305 events) than in patients in the placebo group (48.1% [n=39], 112 events). HLTs occurring in ≥ 10% of patients in either of the two treatment groups (Prochymal vs placebo) were: 'potassium imbalance' (28.8% vs 14.8%); 'hyperglycaemic conditions NEC' (20.2% vs 13.6%); 'magnesium metabolism disorders' (17.8% vs 14.8%); 'total fluid volume increased' (14.7% vs 8.6%); 'sodium imbalance' (12.9% vs 11.1%); 'appetite disorders' (10.4% vs 6.2%); and 'protein metabolism disorders' (9.2% vs 12.3%).

TEAEs (PT) reported as occurring in ≥ 5% of patients in the Prochymal group and ≥ 2% more commonly than in the placebo group were: hypokalaemia (21.5% vs 13.6%); hyperglycaemia (20.2% vs 13.6%); hypomagnesaemia (16.0% vs 11.1%); hyperkalaemia (12.3% vs 4.9%); fluid overload (9.8% vs 4.9%); back pain (9.2% vs 6.2%); anorexia (8.0% vs 0%); hypophosphataemia (7.4% vs 2.5%); hypoglycaemia (7.4% vs 4.9%); and dehydration (6.1% vs 2.5%).

SAEs 'metabolism and nutrition disorders' (SOC) leading to death were reported in 1 (0.6%) patient in the Procyhmal group (0.6%) and no (0%) patients in the placebo group. The SAE (PT) leading to death in the Prochymal group was failure to thrive (x1). SAEs (all) 'metabolism and nutrition disorders' (PT) were reported in 7.4% of patients in the Prochymal group and no (0%) patients in the placebo group. There were no SAEs (PT) reported as occurring in ≥ 2% of patients in the Prochymal group and ≥ 1% more commonly than in the placebo group.

8.5.1.2. Psychiatric disorders

In Protocol 280, 'psychiatric disorders' (SOC) occurred notably more commonly in patients in the Prochymal group (54.6% [n=89], 89 events) than in patients in the placebo group (37.0% [n=30], 44 events). HLTs occurring in ≥ 10% of patients in either of the two treatment groups (Prochymal vs placebo) were: 'confusion and disorientation' (19.0% vs 7.4%); 'anxiety

symptoms' (18.4% vs 6.2%); 'disturbances in initiating and maintaining sleep' (14.1% vs 7.4%); and 'depressive disorders' (11.0% vs 8.6%). TEAEs (PT) reported as occurring in ≥ 5 % of patients in the Prochymal group and ≥ 2% more commonly than in the placebo group were: confusional state (17.2% vs 7.4%); insomnia (14.1% vs 7.4%); anxiety (14.1% vs 6.2%); depression (11.0% vs 8.6%); mental status changes (9.8% vs 6.2%); and agitation (6.1% vs 2.5%).

There were no SAE 'psychiatric disorders' (SOC) leading to death in either treatment group. SAEs (all) 'psychiatric disorders' (PT) were reported in 3.1% patients in the Prochymal group and 2.5% of patients in the placebo group. There were no SAEs (PT) reported as occurring in ≥ 2% of patients in the Prochymal group and ≥ 1% more commonly than in the placebo group.

8.5.1.3. Respiratory disorders

In the preclinical studies, dose limiting toxicity was due to the accumulation of MSCs in the microvasculature of the lungs leading to breathing difficulties and 'pulmonary collapse'. However, in Protocol 280 'respiratory, thoracic and mediastinal disorders' (SOC) were reported in a similar proportion of patients in the Prochymal and placebo groups (62.0% and 59.3%, respectively). HLTs occurring in ≥ 10% of patients in either of the two treatment groups (Prochymal vs placebo) were 'breathing abnormalities' (26.4% vs 18.5%) and 'coughing and associated symptoms' (19.0% vs 16.0%). TEAEs (PT) reported as occurring in ≥ 5% of patients in the Prochymal group and ≥ 2% more commonly than in the placebo group were: dyspnoea (18.4% vs 12.3%); hypoxia (12.3% vs 4.9%); respiratory failure (9.8% vs 6.2%); and rales (6.7% vs 2.5%).

SAEs 'respiratory, thoracic and mediastinal disorders' (SOC) leading to death were reported in 14 (8.6%) patients in the Procyhmal group and 4 (4.9%) patients in the placebo group. The SAEs (PT) leading to death in the Prochymal group were respiratory failure (x6), acute respiratory failure (x2), acute respiratory distress syndrome (x3), respiratory distress (x1), pulmonary haemorrhage (x1), and interstitial lung disease (x1), and in the placebo group were respiratory failure (x1), acute respiratory distress syndrome (x1), respiratory distress (x1), and pulmonary haemorrhage (x1). SAEs (all) 'respiratory, thoracic and mediastinal disorders' (PT) were reported in 18.4% of patients in the Prochymal group and 19.8% of patients in the placebo group. There only SAEs (PT) reported as occurring in ≥ 2% of patients in the Prochymal group and ≥ 1% more commonly than in the placebo group was respiratory distress excluding neonatal (2.5% vs 1.2%).

There were no marked differences between the two treatment groups in oxygen saturation (%) over the course of the study. The PI recommends that oxygen saturation be monitored by pulse oximetry during infusion and this is considered to be an appropriate precaution.

8.5.1.4. Infections and infestations

In Protocol 280, 'infections and infestations' were the most commonly occurring SOC disorders occurring in both treatment groups (Prochymal 88.3%, n=144; placebo 81.5%, n=66). Both treatment groups included numerous HLT and PT 'infections and infestations' events. HLTs occurring in ≥ 10% of patients in either of the two treatment groups (Prochymal vs placebo) were: staphylococcal infections (25.8% vs 14.8%); sepsis, bacteraemia, viraemia and fungaemia NEC (24.5% vs 23.5%); cytomegalovirus infections (23.9% vs 23.5%); bacterial infections NEC (17.8% vs 11.1%); enterococcal infections (15.3% vs 16.0%); lower respiratory tract and lung infections (13.5% vs 13.6%); candida infections (12.3% vs 8.6%); klebsiella infections (11.7% vs 6.2%); and fungal infections NEC (11.0% vs 4.9%).

TEAEs (PT) reported as occurring in ≥ 5% of patients in the Prochymal group and ≥ 2% more commonly than in the placebo group were: cytomegalovirus infection (16.0% vs 13.6%); staphylococcal bacteraemia (12.9% vs 6.2%); pneumonia (12.9% vs 7.4%); sepsis (11.7% vs 7.4%); staphylococcal infection (9.8% vs 6.2%); BK virus infection (9.2% vs 6.2%); enterococcal bacteraemia (6.1% vs 1.2%); candidiasis (5.5% vs 2.5%); and cellulitis (6.1% vs 2.5%).

In both treatment groups, the most commonly occurring SAEs leading to death were 'infections and infestations' (SOC) (Prochymal 25.8%; placebo 14.8%). The proportion of patients with at least 1 SAE (all) categorised as 'infections and infestations' (SOC) was 52.1% in the Prochymal group and 50.6% in the placebo group. SAEs (PT) reported as occurring in ≥ 2% of patients in the Procyhmal group and ≥ 1% more commonly than in the placebo group were: sepsis (8.6% vs 7.4%); pneumonia (6.1% vs 3.7%); bacteraemia (5.5% vs 3.7%); adenovirus infection (3.1% vs 1.2%); staphylococcal bacteraemia (2.5% vs 1.2%); and klebsiella bacteraemia (2.5% vs 1.2%).

8.5.2. Safety in special populations

The data in Protocol 280 and Protocol 275 suggest that the safety profile of Prochymal in adults (aged ≥ 18 years) is similar to that in children and adolescents (aged < 18 years). There were no specific safety data for elderly patients aged ≥ 65 years (in Protocol 280 there were 15 elderly patients and the study excluded patients aged > 70 years), or for patients from different racial groups. There were no separate safety data for males and females.

8.5.3. Safety related to drug-drug and other interactions

There were no safety data relating to drug-drug and other interactions.

8.5.4. Other

There were no clinical safety data relating to rebound or withdrawal effects associated with Prochymal for the treatment of acute GVHD. There were no clinical data relating to the effects of overdose with Prochymal.

8.6. Evaluator's overall conclusions on clinical safety

The submission included safety data on 163 patients treated with Prochymal from protocol 280 (149 adults; 14 children and adolescents), 59 patients from Protocol 275 (children and adolescents), and 12 patients (children and adolescents) from single-patient, emergency use protocols. Overall, the safety profile of Prochymal was similar in adult and paediatric populations. Consequently, the summary of safety will focus on the randomised, placebo-controlled, double-blind data on the 163 patients from Protocol 280 aged from 6 months to 70 years (inclusive).

8.6.1. Protocol 280

The mean total cumulative Prochymal dose was 17.7 ± 6.1 x 10^6 hMSC/kg, the mean ± SD extent of exposure was 36.0 ± 18.6 days in Prochymal group and 31.7 ± 17.5 days in the placebo group, and more than 8 infusions were received by 39.9% and 32.1% of patients in the two treatment groups, respectively. Overall, it is considered that the exposure to Prochymal for the treatment of corticosteroid resistant acute GVHD is sufficient to adequately characterise the safety profile of the product for the proposed indication.

In both the treatment groups, all patients experienced at least 1 TEAE (3165 events in 163 patients in the Prochymal group, and 1376 events in the 81 patients in the placebo group). The large number of TEAEs in both treatment groups in Protocol 280 reflects the serious, life-threatening nature of corticosteroid resistant acute GVHD. Furthermore, in addition to Prochymal or placebo all patients received standard therapies (determined by individual study sites) for the disease.

The main safety concerns associated with Prochymal compared with placebo relate to the higher incidence of adverse events categorised as 'infections and infestations' (primarily staphylococcal bacteraemia, pneumonia, enterococcal bacteraemia); 'metabolism and nutrition disorders' (primarily hypokalaemia, hyperglycaemia, hyperkalaemia, and anorexia); 'respiratory, thoracic and mediastinal disorders' (primarily dyspnoea, and hypoxia); 'psychiatric disorders' (primarily confusional state, anxiety, agitation, and insomnia); 'skin and subcutaneous tissue disorders (primarily rash); 'immune system disorders' (primarily those

related to transplant rejection due to GVHD and acute GVHD in intestine); 'cardiac disorders' (primarily those related to rate and rhythm disorders of atrial fibrillation and tachycardia); and the 'vascular disorder' of hypertension.

The most commonly reported SOC disorders occurring in at least 40% of patients in either group (Prochymal vs placebo) were: Infections and Infestations (88.3% and 81.5%); Gastrointestinal Disorders (74.2% and 77.8%); General Disorders and Administration Site Conditions (68.1% vs 69.1%); Metabolism and Nutrition Disorders (67.5% vs 48.1%); Respiratory, Thoracic and Mediastinal Disorders (62.0% vs 59.3%); Psychiatric Disorders (54.6% vs 37.0%); Investigations (49.7% vs 45.7%); Blood and Lymphatic System Disorders (45.4% vs 34.6%); Skin and Subcutaneous Tissue Disorders (43.6% vs 35.8%); Nervous System Disorders (41.1% vs 46.9%); Musculoskeletal and Connective Tissue Disorders (42.3% vs 44.4%); and Renal and Urinary Disorders (39.9% vs 40.7%).

The most frequently reported TEAEs (PT) occurring in ≥ 20% of patients in either treatment group (Prochymal vs placebo) were: peripheral oedema (35.6% vs 33.3%); abdominal pain (22.7% vs 17.23%); thrombocytopenia (22.1% vs 22.2%); hypokalaemia (21.5% vs 13.6%); diarrhoea (22.9% vs 18.5%); hyperglycaemia (20.2% vs 13.6%); and pyrexia (20.2% vs 17.3%). In both treatment groups, the majority of patients experienced NCI CTCAE Grade 3 or higher events (93.9%, Prochymal; 92.6%, placebo).

TEAEs (PT) occurring ≥ 5% more commonly in patients in the Prochymal group than in patients in the placebo group and listed from highest to lowest absolute difference between the two treatment groups were: (1) confusion and disorientation 11.6% (19.0% vs 7.4%); (2) hypertension 10.4% (17.8% vs 7.4%); (3) confusional state 9.8% (17.2% vs 7.4%); (4) anorexia 8.0% (8.0% vs 0%); (5) anxiety 7.9% (14.1% vs 6.2%) and hypokalaemia 7.9% (21.5% vs 13.6%); (6) hyperkalaemia 7.4% (12.3% vs 4.9%); (7) abdominal distension 7.3% (9.8% vs 2.5%); (8) staphylococcal bacteraemia 6.7% (12.9% vs 6.2%), tremor 6.7% (12.9% vs 6.2%), and insomnia 6.7% (14.1% vs 7.4%); (9) hyperglycaemia 6.6% (20.2% vs 13.6%); (9) mucosal inflammation 6.2% (7.4% vs 1.2%); (10) dyspnoea 6.1% (18.4% vs 12.3%); (11) dizziness 5.5% (5.5% vs 0%), pneumonia 5.5% (12.9% vs 7.4%), haematochezia 5.5% (5.5% vs 0%), and rash 5.5% (11.7% vs 6.2%); (12) abdominal pain 5.4% (22.7 vs 17.3%).

The proportion of patients who experienced at least 1 SAE was 89.5% (n=146) in the Prochymal group and 87.7% (n=71) in the placebo group. In the safety population, the proportion of patients with SAEs leading to death (NCI CTCAE Grade 5) was higher in the Prochymal group (64.4%) than in the placebo group (54.3%). In both treatment groups, death was primarily due to 'infections and infestations' (Prochymal 25.8%; placebo 14.8%, n=12). The only other SOC group of disorders resulting in ≥ 10% of deaths in at least one of the treatment groups was 'immune system disorders' (Prochymal 14.1%; placebo 6.2%, n=5).[6]

The most commonly reported SAEs (PT), including those that resulted in death, occurring in ≥ 5% of patients in either treatment group (Prochymal vs placebo) listed by decreasing frequency in the Prochymal group were: GVHD (14.7% vs 11.1%); gastrointestinal haemorrhage (7.4% vs 6.2%); sepsis (8.6% vs 7.4%); GVHD in intestine (6.7% vs placebo 3.7%); pneumonia (6.1%, vs 3.7%); respiratory failure (6.1% vs 6.2%); bacteraemia (5.5% vs 3.7%), and multi-organ failure (2.5% vs 7.4%).

SAEs (PT), including those that resulted in death, occurring in ≥ 2% and < 5% of patients in the Prochymal group, and with equal or greater frequency compared with the placebo group were: pyrexia (3.7% vs 3.7%); adenovirus infection (3.1% vs 1.2%); acute myeloid leukemia (3.1% vs 2.5%); renal failure (3.1% vs 2.5%); atrial fibrillation (2.5% vs 1.2%); septic shock (2.5% vs 2.5%); cytomegalovirus infection (2.5%, vs 2.5%); staphylococcal bacteraemia (2.5% vs 1.2%);

[6] Immune system disorders include Graft versus Host Disease, which is the disease present at study entry/baseline.

klebsiella bacteremia (2.5% vs 1.2%); renal failure acute (2.5% vs 2.5%); and respiratory distress (2.5% vs 1.2%).

Permanent discontinuation due to TEAEs was reported in 9.2% of patients in the Prochymal group and 13.6% of patients in the placebo group. There were a total of 30 TEAEs (PT) reported as leading to discontinuation in one or both of the two treatment groups. The only TEAE (PT) reported as leading to discontinuation in more than 1 patient in either of the two treatment groups was hypoxia (3 patients in the Prochymal group).

TEAEs and SAEs associated with infusional toxicity were uncommon in both treatment groups (1.8% and 2.5% of patients in the Prochymal and placebo groups, respectively). There were no TEAEs related to ectopic tissue formation in either of the two treatment groups. TEAEs indicative of relapse of underlying disease were reported in a similar proportion of patients in the Prochymal (8.0%) and the placebo (9.9%) treatment groups. There were no marked differences between the two treatment groups as regards clinical laboratory tests, vital signs, or ECG results.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

It is considered that the data from Protocol 280 have failed to satisfactorily establish the efficacy of Prochymal compared with placebo for the treatment of corticosteroid refractory acute GVHD (i.e., no significant treatment benefit for Prochymal has been demonstrated). In addition, the apparent benefits of Prochymal treatment in a paediatric population aged < 18 years observed in Protocol 275, and in the 12 patients treated according to single-patient, emergency use protocols cannot be meaningfully interpreted due to the absence of placebo control groups in these protocols.

In Protocol 280, the primary efficacy endpoint of complete response of ≥ 28 days duration in the overall ITT population (Grade B/C/D) was 34.7% (60/173) in the Prochymal group and 29.9% (26/87) in the placebo group; p = 0.423 (CMH test stratified by GVHD grade at diagnosis/study entry). Similarly, there were no statistically significant differences between Prochymal and placebo for the secondary efficacy endpoints of survival at 100 days and survival at 180 days post-infusion in the mITT population. The proportion of patients surviving for > 100 days in the Prochymal and placebo groups was 52.1% (85/163) and 50.6% (41/81), respectively (p=0.780). The proportion of patients surviving for > 180 days in the Prochymal and placebo groups was 34.4% (56/163) and 42.0% (34/81), respectively (p = 0.274).

Based on expert consensus opinion, the sponsor (Osiris) considers that OR at Day 28 (following the first Prochymal infusion) is the most clinically meaningful efficacy outcome in clinical trials designed to assess the effects of treatment for acute GVHD. However, OR at Day 28 was not specified as either a primary or secondary efficacy endpoint in Protocol 280, but was mentioned in the CSR as an additional/exploratory endpoint. Furthermore, in Protocol 280 there was no statistically significant difference between Prochymal and placebo in OR response at Day 28 in the overall acute GVHD (Grade B/C/D) population (57.7% [94/163] and 50.6% [41/18], respectively, p = 0.224).

In Protocol 275, the primary efficacy outcome was OR at Day 28 in a paediatric population aged < 18 years treated with Prochymal. In this protocol, the OR at Day 28 in the Prochymal group was 62.7% (37/59) in the overall patient population (acute GVHD B-D). However, the clinical significance of this apparent benefit is difficult to interpret because of the absence of a placebo comparator group. It is considered that the OR at Day 28 results observed in Protocol 280 highlight the importance of having a placebo control comparator group when interpreting the outcomes for this endpoint (i.e., no statistically significant difference between Prochymal and

placebo, and a high placebo response rate observed in Protocol 280). Furthermore, while the protocol specified time window for the assessment of OR at Day 28 was ± 2 days, the provided result included data from patients assessed from 20 to 38 days inclusive. Consequently, the reported OR at Day 28 is potentially higher than that which would have been observed if the specified time window of ± 2 days had been used to calculate the endpoint.

The submission included a comparison between the Kaplan-Meier probabilities of survival for 180 days for patients in Protocol 275 (Prochymal) and a 'historical control' (external benchmark) of paediatric patients with acute GVHD Grade II-IV from the CIBMTR database. This comparison showed that the probabilities of 180 day survival for patients with maximum GVHD Grade C were 69.0% [95% CI: 64.0, 74.0] in the historical control group and 87.1% [95% CI: 70.3, 100] in the Prochymal group, and for patients with maximum GVHD Grade D the corresponding figures were 31.0% [95% CI: 26.0-36.0] in the historical control group and 56.2% [CI: 40.5-71.8] in the Prochymal group. Patients who had received Prochymal had a statistically significantly higher probability of survival compared with the historical control (p = 0.003). However, it should be noted that in Protocol 280 there was no statistically significant difference between Prochymal and placebo in the proportion of patients surviving for > 180 days.

9.2. First round assessment of risks

Overall, the data from Protocol 280 suggest that the safety profile of Prochymal is inferior to that of placebo in a number of respects. TEAEs (PT) reported in ≥ 5% more patients in the Prochymal group compared with the placebo group observed in Protocol 280 are listed below. The absolute difference between the two treatment groups is provided as are the results for each treatment group (Prochymal vs placebo):

- confusion and disorientation 11.6% (19.0% vs 7.4%)
- hypertension 10.4% (17.8% vs 7.4%)
- confusional state 9.8% (17.2% vs 7.4%)
- anorexia 8.0% (8.0% vs 0%)
- anxiety 7.9% (14.1% vs 6.2%) and hypokalaemia 7.9% (21.5% vs 13.6%)
- hyperkalaemia 7.4% (12.3% vs 4.9%)
- abdominal distension 7.3% (9.8% vs 2.5%)
- staphylococcal bacteraemia 6.7% (12.9% vs 6.2%), tremor 6.7% (12.9% vs 6.2%), and insomnia 6.7% (14.1% vs 7.4%)
- hyperglycaemia 6.6% (20.2% vs 13.6%)
- mucosal inflammation 6.2% (7.4% vs 1.2%)
- dyspnoea 6.1% (18.4% vs 12.3%)
- dizziness 5.5% (5.5% vs 0%), pneumonia 5.5% (12.9% vs 7.4%), haematochezia 5.5% (5.5% vs 0%), rash 5.5% (11.7% vs 6.2%) and
- abdominal pain 5.4% (22.7 vs 17.3%).

The most notable difference in TEAEs (SOC) between the two treatment groups was the higher incidence of 'psychiatric disorders' in the Prochymal group (54.6%) compared with the placebo group (37.0%). The difference between the two groups related particularly to the higher incidence of confusional state, anxiety and insomnia in the Prochymal group than in the placebo group. These are unusual and unexpected finding for this product and appear to be unrelated to possible confounders such as high dose corticosteroid use. Furthermore, Protocol 280

specifically excluded patients with underlying or current psychiatric conditions. In addition, there was no marked difference in baseline history of psychiatric disorders between the Prochymal group (50.3%) and the placebo group (47.1%). However, TEAEs categorised as 'psychiatric disorders' and leading to treatment discontinuation were uncommon in patients in the Prochymal (1 [0.6%] x disorientation; 1 [0.6%] x catatonia; 1 [0.6%] x delirium; 1 x [0.6%] mental state change), while no discontinuations related to this group of disorders were reported in the placebo group. In addition, there were no SAE 'psychiatric disorders' (SOC) leading to death in either treatment group. SAEs (all) 'psychiatric disorders' (PT) were reported in 3.1% patients in the Prochymal group and 2.5% of patients in the placebo group, but there were no SAEs (PT) reported as occurring in ≥ 2% of patients in the Prochymal group and ≥ 1% more commonly than in the placebo group.

Two other unexpected TEAEs occurring with higher incidences in the Prochymal group compared with the placebo group were hypertension and hyperglycaemia. The was no difference between the two treatment groups as regards baseline medical history of hypertension (46.8% vs 46.0%, Prochymal and placebo groups, respectively) or hyperglycaemia (38.2% vs 47.1%, Prochymal and placebo groups, respectively). However, a baseline medical history of diabetes mellitus (including subtypes) was notably more common in the Prochymal group (13.3%) than in the placebo group (5.7%).

The proportion of patients in the safety population who experienced at least 1 SAE was similar in the Prochymal (89.6%) and placebo groups (87.7%). However, the risk of death in the safety population was greater in the Prochymal group than in the placebo group (64.4% vs 54.3%, respectively), primarily due to 'infections and infestations' (25.8% vs 14.8%), and 'immune system disorders' (14.1% vs 6.2%). The difference between the two treatment groups (safety population) in the risk of death are consistent with the lower > 180 day survival rate in patients (mITT population) in the Prochymal group compared with patients in the placebo group (34.4% vs 42.0%, respectively; p=0.274).

The most notable difference between the two treatment groups as regards deaths due to 'infections and infestations' (SOC) related to the HLT of 'sepsis, bacteraemia, viraemia, and fungaemia NEC' which was reported in 8.0% of patients in the Prochymal group and 4.9% of patients in the placebo group. Deaths occurred notably more commonly in the Prochymal group than in the placebo group in the TEAEs (HLTs) of cytomegaloviral infections (3.1% vs 0%), adenoviral infections (3.1% vs 1.2%), aspergillus infections (2.5% vs 0%), fungal infections (1.8% vs 0%), and pseudomonal infections (1.8% vs 0%). The most notable difference between the two treatment groups as regards deaths due to 'immune system disorders' (SOC) related to the TEAE (PT) of GVHD which was reported in 9.8% of patients in the Prochymal group and 4.9% of patients in the placebo group.

SAEs (all) occurring in ≥ 2% of patients in the Prochymal group and more frequently than in the placebo group were: GVHD (14.7% vs 11.1%); gastrointestinal haemorrhage (7.4% vs 6.2%); sepsis (8.6% vs 7.4%); GVHD in intestine (6.7% vs placebo 3.7%); pneumonia (6.1%, vs 3.7%); bacteraemia (5.5% vs 3.7%); adenovirus infection (3.1% vs 1.2%); acute myeloid leukemia (3.1% vs 2.5%); renal failure (3.1% vs 2.5%); atrial fibrillation (2.5% vs 1.2%); staphylococcal bacteraemia (2.5% vs 1.2%); klebsiella bacteraemia (2.5% vs 1.2%); and respiratory distress (2.5% vs 1.2%).

Discontinuations due to TEAEs were reported more commonly in the placebo group than in the Prochymal group (13.6% and 9.2%, respectively). There were no marked differences between the two treatment groups as regards haematological, hepatic or renal toxicity, but cardiac disorders occurred more commonly in the Prochymal group than in the placebo group (predominantly due to tachycardia and atrial fibrillation). In Protocol 280, there were no notable differences between the two treatment groups as regards changes in vital signs and ECG findings over the course of the study.

There are no safety data relating to interactions between Prochymal and other medicines. There are no data on the safety of Prochymal specifically in elderly patients (aged ≥ 65 years), or separately in males and females. There are no safety data relating to rebound or withdrawal effects following discontinuation of Prochymal.

9.3. First round assessment of benefit-risk balance

The benefit-risk balance for Prochymal for the proposed usage is considered to be unfavourable. The submitted data have failed to demonstrate a meaningful clinical benefit in patients with corticosteroid resistant acute GVHD treated with Prochymal compared with placebo, and the risks of treatment with Prochymal for the proposed usage are considered to be greater than those of placebo.

10. First round recommendation regarding authorisation

It is recommended that the application to register Prochymal for the proposed indication be rejected on the grounds of inadequate demonstration of efficacy. The reasons for this recommendation are as follows:

1. The failure of Protocol 280 (pivotal study) to demonstrate a statistically significant difference between Prochymal and placebo for the primary efficacy endpoint of complete response of ≥ 28 days duration in the overall ITT population (acute GVHD Grade B/C/D): i.e., 34.7% (60/173) and 29.9% (26/87), respectively, p = 0.423.
2. The failure of Protocol 280 (pivotal study) to demonstrate a statistically significant difference between Prochymal and placebo for the secondary efficacy endpoint of overall survival > 100 days in the overall mITT population (acute GVHD Grade B/C/D): i.e., 52.1% (85/163) and 50.6% (41/81), respectively, p = 0.780.
3. The failure of Protocol 280 (pivotal study) to demonstrate a statistically significant difference between Prochymal and placebo in the secondary efficacy endpoint of overall survival > 180 days in the overall mITT population (acute GVHD Grade B/C/D): i.e., 34.4% (56/163) and 42.0% (34/81), respectively, p = 0.274.
4. The lack of a placebo control group in Protocol 275 (supportive study) making it difficult to interpret the clinical significance of the observed overall response rate at day 28 of 62.7% (37/59) in a paediatric population aged < 18 years (i.e., the primary efficacy endpoint). The importance of including a placebo control group when assessing the efficacy of Prochymal is highlighted by the results from Protocol 280 for overall response at day 28 which failed to show a statistically significant difference between the two treatment groups: i.e., 57.7% (94/163) in the Prochymal group compared with 50.6% (41/81) in the placebo group, p = 0.224.

11. Clinical questions

11.1. Pharmacokinetics

No questions

11.2. Pharmacodynamics

No questions

11.3. Efficacy

In Protocol 275, the protocol specified that the primary efficacy endpoint of OR was to be assessed at Day 28 ± 2 days. However, the provided results for the OR at Day 28 included assessments undertaken between study days 20 and 38.

- Please explain why the submitted analysis was undertaken on patients assessed outside Day 28 ± 2 days.
- Please justify how the provided assessment of OR at Day 28 (day 20 to day 38) can be considered to be a surrogate for assessment of OR at Day 28 ± 2 days.
- Please provide an analysis of only those patients who had an assessment for OR at Day 28 ± 2 days.

11.4. Safety

No questions

12. Second round evaluation of clinical data submitted in response to questions

12.1. Overview of the second round data

The sponsor's s31 response, dated 30 April 2012, included responses to the clinical questions raised by the TGA following the first round evaluation of the submission. Clinical comments on the sponsor's response are provided. In addition, the TGA quality evaluator has recommended that clinical advice be provided on certain matters referred to in the sponsor's response to first round evaluation quality questions. This advice has been provided. The first and second round clinical evaluation reports have been prepared by the same clinical evaluator, and this evaluator has also provided clinical advice on the matters identified by the TGA quality evaluator.

12.2. Sponsor's response to clinical questions and evaluator's comments

12.2.1. Efficacy (question 1)

In Protocol 275, the protocol specified that the primary efficacy endpoint of OR was to be assessed at Day 28 ± 2 days. However, the provided results for the OR at Day 28 included assessments undertaken between study days 20 and 38:

- Please explain why the submitted analysis was undertaken on patients assessed outside Day 28 ± 2 days.
- Please justify how the provided assessment of OR at Day 28 (day 20 to day 38) can be considered to be a surrogate for assessment of OR at Day 28 ± 2 days.
- Please provide an analysis of only those patients who had an assessment for OR at Day 28 ± 2 days.

12.2.1.1. Sponsor's (Osiris) response:

In Protocol 275, the Prochymal treatment regimen is 8 infusions, each infusion given 3-4 days apart, for a treatment period of about 24-25 days. In the original version of the protocol, dated 04Jun2007, the first GvHD assessment was set at Day 32 ± 2 days, one week after the 8th infusion, since the practice of most clinical sites is to assess GvHD status on a weekly basis. There was then a growing consensus in the GvHD community that Overall Response at Day 28 is the optimal endpoint for assessing treatment effect in acute GvHD. This consensus was

subsequently endorsed by the experts of a FDA/CIBMTR workshop on clinical endpoints in acute GvHD. As a result, the protocol was amended to adjust the GvHD assessment from Day 32 ± 2 days to Day 28 ± 2 days (Amendment 1 dated 14 March 2008).

Out of 59 patients, thirty-six patients completed their GvHD assessment according to protocol (Day 28 ± 2 or Day 32 ± 2) (Table 11).

Table 11: GvHD assessment data

GvHD Assessment (days)	Number of Patients	OR	Comments
32 ± 2 days	8	7/8 (87.5%)	Original protocol
28 ± 2 days	28	19/28 (67.9%)	Protocol Amendment 1 onwards
24-25 days	12	9/12 (75.0%)	Site performed assessment at last infusion of the initial treatment schedule visit
21-38 days	5	2/5 (40.0%)	These patients completed a full GvHD assessment out of protocol window
None (death prior to Day 28)	6	n/a (non-responders)	Patients died and an end-of-study evaluation page was completed
Total	59	37/59 (62.7%)	

For forty-two patients (71%), the GvHD assessments were performed according to protocol. An additional twelve patients had the GvHD assessment performed immediately after the last Prochymal infusion (Day 24-25). Of importance, all of these patients (54/59, 92%) received the full treatment course of 8 infusions or died prior to reaching Day 28. The treatment compliance for these fifty-four patients is 100%. The GvHD status for these patients represents a good assessment of the effect of a full course of Prochymal infusions.

Five patients underwent the GvHD assessment in a 21 to 38 day window. These assessments were completed outside the recommended protocol window for a variety of reasons, some related to the compromised nature of these very sick patients and some related to the physician's request for continued therapy. Of these five patients, one patient died at Day 21 after 6 infusions. The patient had completed a full GvHD assessment the day of death and was included in the analysis. The patient was a non-responder. Another patient completed the GvHD assessment at day 22 after 7 infusions. The patient was a partial responder and the physician requested continued therapy. A third patient had the GvHD status assessed at Day 23 after 8 infusions, was a partial responder and also continued therapy. A fourth patient had the GvHD assessment at Day 31 after 8 infusions. The assessment was conducted on a Monday (Day 31) and according to the window should have been done the Friday before (Day 28). A fifth patient was evaluated after 8 infusions at 38 days, and reasons for the delay are unknown.

12.2.1.2. Clinical evaluators' comment

The sponsor's response is satisfactory and has clarified the assessment of Prochymal treatment in supportive Protocol 275. The primary efficacy endpoint in this protocol was ORR (CR + PR) at day 28. The day 28 assessment was based on response data reported between days 20 and 38 from all 59 patients, and included patients who died before day 28 as non-responders. The ORR in patients with GVHD B-D in the primary efficacy analysis was 62.7% (37/59).

The sponsor's s31 additional data show that in patients analysed at 28 ± 2 days the OR was 67.9% (19/28), and in patients analysed at 32 ± 2 days the OR was 87.5% (7/8). However, assessments at these time points were aimed at determining whether further treatment was indicated and excluded patients who had died prior to assessment. Therefore, the OR analyses at these time points are not comparable to the primary efficacy analysis of the OR in which patients who had died were included in the assessment as non-responders. The primary efficacy endpoint analysis is considered to be a reasonable clinical measure of overall response to treatment as it includes relevant response data from all 59 treated patients. However, it is noted that if response is assessed at day 28±2, and includes patients who died prior to day 28 as non-

responders, then the OR is 55.9% (19/34) which is lower than the OR in the primary analysis (62.7%; 37/59). Overall, the additional data submitted by the sponsor do not alter the first round assessment of the benefits or the benefit-risk balance of Prochymal for the proposed indication.

12.3. Requested clinical advice on responses to first round quality assessment

12.3.1. Toxicity of infused dead cells

The TGA quality evaluator has requested clinical advice on the whether the toxicity of infused dead cells has been sufficiently addressed. The TGA quality evaluator notes that 'it is not stated in the dossier, but within the undifferentiated MSC population (≥ 95% of the cells) there may be MSC subpopulation types (antigenically defined or otherwise). It is evident the current literature has not fully defined the MSC subpopulations or provided standardised criteria for their characterisation. Provided there is an assurance of a consistent and reproducible manufacturing process, there is unlikely to be a basis on quality grounds for requesting a further definition of Prochymal in relation to its MSC population subtypes. With respect to other viable cell-based impurities, these may include viable CD45+ cells and other undefined CD45-/CD105-/CD166- cells (<5%), which may be retained through the process of mononuclear cell isolation, plastic culture plate adherence, trypsinisation and cell washes over 5 passages in culture'.

12.3.1.1. Clinical evaluator's comment

The first-round risks of treatment with Prochymal are summarised in Section 9.3 of this CER. This assessment was primarily based on the placebo-controlled data from Protocol 280. Overall, it is considered that the risks of treatment with Prochymal have been adequately characterised in Protocol 280. The patient numbers in Protocol 280 were small in both the Prochymal (n=163) and placebo (n=81) treatment groups, but this is not unexpected given that Prochymal is a designated orphan drug. If the Prochymal formulation used in Protocol 280 notably differs from that being proposed for registration, then the risks of treatment with the proposed formulation might differ from those observed in Protocol 280.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

After consideration of the responses to clinical questions, the wording of the benefits of Prochymal in the proposed usage have been amended to delete speculation on the effect of potential differences in response between the primary efficacy analysis and the efficacy analysis at 28 ± 2 days. The second round assessment of benefits follows:

It is considered that the data from Protocol 280 have failed to satisfactorily establish the efficacy of Prochymal compared with placebo for the treatment of corticosteroid refractory acute GVHD (i.e., no significant treatment benefit for Prochymal has been demonstrated). In addition, the apparent benefits of Prochymal treatment in a paediatric population aged < 18 years observed in Protocol 275, and in the 12 patients treated according to single-patient, emergency use protocols cannot be meaningfully interpreted due to the absence of placebo control groups in these protocols.

In Protocol 280, the primary efficacy endpoint of complete response of ≥ 28 days duration in the overall ITT population (Grade B/C/D) was 34.7% (60/173) in the Prochymal group and 29.9% (26/87) in the placebo group; p = 0.423 (CMH test stratified by GVHD grade at diagnosis/study entry). Similarly, there were no statistically significant differences between Prochymal and placebo for the secondary efficacy endpoints of survival at 100 days and survival at 180 days

post-infusion in the mITT population. The proportion of patients surviving for > 100 days in the Prochymal and placebo groups was 52.1% (85/163) and 50.6% (41/81), respectively (p=0.780). The proportion of patients surviving for > 180 days in the Prochymal and placebo groups was 34.4% (56/163) and 42.0% (34/81), respectively (p = 0.274).

Based on expert consensus opinion, the sponsor (Osiris) considers that OR at Day 28 (following the first Prochymal infusion) is the most clinically meaningful efficacy outcome in clinical trials designed to assess the effects of treatment for acute GVHD. However, OR at Day 28 was not specified as either a primary or secondary efficacy endpoint in Protocol 280, but was mentioned in the CSR as an additional/exploratory endpoint. Furthermore, in Protocol 280 there was no statistically significant difference between Prochymal and placebo in OR response at Day 28 in the overall acute GVHD (Grade B/C/D) population (57.7% [94/163] and 50.6% [41/18], respectively, p = 0.224).

In Protocol 275, the primary efficacy outcome was OR at Day 28 in a paediatric population aged < 18 years treated with Prochymal. This assessment was based on outcomes over a broad window of from 20 to 38 days. In this protocol, the OR at 'Day 28' in the Prochymal group was 62.7% (37/59) in the overall patient population (acute GVHD B-D). However, the clinical significance of this apparent benefit is difficult to interpret because of the absence of a placebo comparator group. It is considered that the OR at Day 28 results observed in Protocol 280 highlight the importance of having a placebo control comparator group when interpreting the outcomes for this endpoint (i.e., no statistically significant difference between Prochymal and placebo, and a high placebo response rate observed in Protocol 280).

The submission included a comparison between the Kaplan-Meier probabilities of survival for 180 days for patients in Protocol 275 (Prochymal) and a historical control (external benchmark) of paediatric patients with acute GVHD Grade II-IV from the CIBMTR database. This comparison showed that the probabilities of 180 day survival for patients with maximum GVHD Grade C were 69.0% [95% CI: 64.0, 74.0] in the historical control group and 87.1% [95% CI: 70.3, 100] in the Prochymal group, and for patients with maximum GVHD Grade D the corresponding figures were 31.0% [95% CI: 26.0-36.0] in the historical control group and 56.2% [CI: 40.5-71.8] in the Prochymal group. Patients who had received Prochymal had a statistically significantly higher probability of survival compared with the historical control (p = 0.003). However, it should be noted that in Protocol 280 there was no statistically significant difference between Prochymal and placebo in the proportion of patients surviving for > 180 days.

13.2. Second round assessment of risks

After consideration of the responses to clinical questions, the risks of Prochymal in the proposed usage are unchanged from those identified in Section 9.2.

13.3. Second round assessment of benefit-risk balance

After consideration of the responses to clinical questions, the benefit risk-balance of Prochymal in the proposed usage are unchanged from those identified in Section 9.3. The benefit-risk benefit remains unfavourable for the reasons provided in Section 9.3.

14. Second round recommendation regarding authorisation

It is recommended that the application to register Prochymal for the proposed indication be **rejected** on the grounds of inadequate demonstration of efficacy. The reasons for this recommendation are as follows:

1. The failure of Protocol 280 (pivotal study) to demonstrate a statistically significant difference between Prochymal and placebo for the primary efficacy endpoint of complete response of ≥ 28 days duration in the overall ITT population (acute GVHD Grade B/C/D): i.e., 34.7% (60/173) and 29.9% (26/87), respectively, p = 0.423.
2. The failure of Protocol 280 (pivotal study) to demonstrate a statistically significant difference between Prochymal and placebo for the secondary efficacy endpoint of overall survival > 100 days in the overall mITT population (acute GVHD Grade B/C/D): i.e., 52.1% (85/163) and 50.6% (41/81), respectively, p = 0.780.
3. The failure of Protocol 280 (pivotal study) to demonstrate a statistically significant difference between Prochymal and placebo in the secondary efficacy endpoint of overall survival > 180 days in the overall mITT population (acute GVHD Grade B/C/D): i.e., 34.4% (56/163) and 42.0% (34/81), respectively, p = 0.274.
4. The lack of a placebo control group in Protocol 275 (supportive study) making it difficult to interpret the clinical significance of the observed overall response rate at 'day 28' of 62.7% (37/59) in a paediatric population aged < 18 years (i.e., the primary efficacy endpoint). The importance of including a placebo control group when assessing the efficacy of Prochymal is highlighted by the results from Protocol 280 for overall response at day 28 which failed to show a statistically significant difference between the two treatment groups: i.e., 57.7% (94/163) in the Prochymal group compared with 50.6% (41/81) in the placebo group, p = 0.224.

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