INVESTIGATORS BROCHURE

SPONSOR:	Dimerix Bioscience Pty Ltd
INVESTIGATIONAL PRODUCT:	DMX-200 (repagermanium) for the treatment of moderate to severe ARDS in patients with suspected or confirmed COVID-19
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Investigator Brochure Approval

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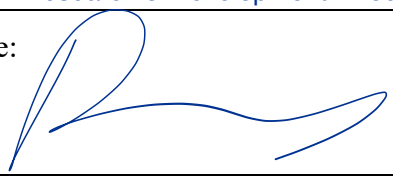
Signature: 

Date: 25 June 2021

LIST OF ABBREVIATIONS

ACE	angiotensin converting enzyme
ACEI	angiotensin converting enzyme inhibitors
ACE1	angiotensin converting enzyme 1
ACE2	angiotensin converting enzyme 2
AE	adverse event
ALI	acute lung injury
ALP	alkaline phosphatase
ALT	alanine aminotransferase
API	active pharmaceutical ingredient
ARB	angiotensin II receptor blockers
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
AT1	angiotensin II type 1
AT1R	angiotensin II type 1 receptor
$AUC_{(0\text{-last})}$	area under the curve from first timepoint to last timepoint
BID	bis in die (2 times daily)
BALF	bronchoalveolar lavage fluid
BMI	body mass index
CAP	community acquired pneumonia
CCR2	chemokine receptor-2
CCR5	chemokine receptor-5
CCL2	C-C motif chemokine ligand 2
CCL3	C-C motif chemokine ligand 3
CCL4	C-C motif chemokine ligand 4
cGMP	current good manufacturing practice
CHL	chinese hamster lung
C_{max}	maximum plasma concentration
COV	coronavirus
COVID-19	viral infection caused by the SARS-Cov2 pathogen
CXCL1	chemokine C-X-C motif ligand 1
CXCL2	chemokine C-X-C motif ligand 2
CXCL6	chemokine C-X-C motif ligand 6
CXCL8	chemokine C-X-C motif ligand 8
CXCL10	chemokine C-X-C motif ligand 10
DKD	diabetic kidney disease
DMX-200	Dimerix's investigational medicinal product (repagermanium)
DSUR	drug safety update report

DUNS	Dun & Bradstreet unique identifier
eGFR	estimated glomerular filtration rate
FDA	Food and Drug Administration
FEI	FDA establishment identification
FGF	fibroblast growth factor
FSGS	focal segmental glomerulosclerosis
GCSF	granulocyte colony stimulating factor
GLP	good laboratory practice
GMCSF	granulocyte macrophage colony stimulating factor
HBeAg	hepatitis B antigen
HED	human equivalent dose
ICH	international conference on harmonisation
ICU	intensive care unit
IFN	interferon
IFN-γ	interferon gamma
IL	interleukin
IL-1B	interleukin 1 beta
IL-1RA	interleukin-1 receptor antagonist
IL-2	interleukin 2
IL-2Rα	interleukin-2 receptor α chain
IL-5	interleukin 5
IL-7	interleukin 7
IL-8	interleukin 8
IL-9	interleukin 9
IL-10	interleukin 10
IP-10	interferon gamma induced protein 10
IMP	Investigational medicinal product
LD50	lethal dose, 50%
MCP-1	monocyte chemoattractant protein-1
MCP	metacarpophalangeal
MCR	microalbumin/creatinine random
MIP-1A	macrophage inflammatory protein 1A
MIP-1B	macrophage inflammatory protein 1B
nCov	novel coronavirus
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NSAID	non-steroidal anti-inflammatories
p	probability value
PCR	protein/creatinine ratio

PDGF	platelet derived growth factor
PMDA	Pharmaceuticals and Medical Devices Agency
RAAS	renin angiotensin aldosterone system
RAS	renin-angiotensin system
RSI	reference safety information
SAE	serious adverse event
SARS	severe acute respiratory syndrome
SAS	special access scheme
SARS-CoV	SARS-associated coronavirus
SARS-CoV2	severe acute respiratory syndrome coronavirus 2
SOC	system organ class
STNx	subtotal nephrectomy
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	biological half life
TDD	total daily dose
TEAE	treatment emergent adverse event
TH1	type 1 T helper cells
TID	ter in die (3 times daily)
t_{max}	time to maximum plasma concentration
TNF	tumor necrosis factor
US	United States of America
US FDA	United States Food and Drug Administration
VAP	ventilator assisted pneumonia
VEGF	vascular endothelial growth factor

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1. SUMMARY

Dimerix is developing DMX-200 (repagermanium) for the inhibition of the C-C motif chemokine receptor 2 (CCR2) in patients already receiving an angiotensin receptor blocker (ARB). The angiotensin II type 1 receptor (AT1R) and CCR2 functionally interact on the cell surface in vitro. (Ayoub 2015). When both receptors and their ligands are present, it is beneficial to simultaneously inhibit both receptors to reduce receptor signalling. When administered concurrently with an ARB, DMX-200 is designed to inhibit inflammation and recruitment of monocytes to areas of inflammation.

DMX-200 (repagermanium) is a small molecule that is delivered orally at a dose of 240 mg per day as 120 mg capsules twice daily (BID) or dissolved in water for gastric tube administration. The drug product is a non-sterile size 2 capsule filled with a formulation containing repagermanium, lactose and magnesium stearate.

All available nonclinical data suggests that repagermanium has a low toxicity, does not share any target organs with ARBs, and the kinetics and metabolism of these compounds do not suggest potential for a detrimental drug-drug interaction. Dimerix has demonstrated that the use of DMX-200 and an ARB acts synergistically to reduce proteinuria and podocyte loss to a greater level compared to inhibition of either receptor alone in the sub-total nephrectomy animal model of renal impairment.

An alternative crystal form of repagermanium is called propagermanium. This molecule is registered with the Japanese Pharmaceuticals and Medical Devices Agency (PDMA) under the brand name Serocion® for the treatment of chronic hepatitis B. The molecule is delivered at a dose of 30 mg daily, and was administered to 2,015 patients with adverse reactions reported in 221 patients (10.97%). The most frequent adverse events (AEs) were elevated aspartate aminotransferase (AST) (1.89%), elevated alanine aminotransferase (ALT) (1.99%), general languor (1.34%), and diminished appetite (0.89%). In the population of patients with hepatitis B, a major adverse reaction of acute exacerbation of chronic hepatitis B has been observed.

Dimerix has completed 4 clinical studies with DMX-200 in N=95 participants in which DMX-200 has been safe and well tolerated. In a Phase 1 study of 2 formulations of 120 mg DMX-200 (120 mg immediate release capsule and 120 mg extended release tablet) in healthy volunteers (N=15), there were no clinically significant events following treatment associated with abnormal laboratory findings, vital signs and electrocardiograms (ECGs). The most common AEs were gastrointestinal disorders with 8 events in 6 participants and 2 participants reported diarrhoea and 2 participants reported vomiting. In a Phase 2a study of patients with proteinuria (N=27), DMX-200 at a dose of 30-240 mg/day was safe and well tolerated when administered to patients already receiving a maximally tolerated dose of the ARB irbesartan. The study demonstrated that there were no clinically significant trends associated with treatment-related adverse events at a daily dose of DMX-200 up to 240 mg. The most frequently reported treatment emergent adverse events (TEAEs) were gout (18.5%), increased plasma creatinine (14.8%), diarrhoea (11.1%) oedema (11.1%), decreased haemoglobin (11.1%). Two Phase 2 trials in primary focal segmental glomerulosclerosis (FSGS, N=8) and diabetic kidney disease (DKD, N=45) have also been completed with a daily dose of DMX-200 of 240 mg. The frequency of TEAEs was similar between the DMX-200 and placebo groups. None of the TEAEs assigned to DMX-200 or placebo were considered treatment-related. The majority of patients experienced TEAEs that were mild or moderate in severity. The most frequently reported adverse drug reactions (ADRs) reported across Dimerix sponsored clinical trials include hyperkalaemia/blood potassium increased (3 ADRs reported by 2 participants [2.1%]). Other ADRs reported by at least 2 participants (2.1%) include

blood creatinine increased, diarrhoea, nausea, oedema peripheral, and pollakiuria. All remaining ADRs were reported by 1 participant only (1.1%).

Simultaneous intervention in AT1R and CCR2 signalling may benefit patients with acute respiratory distress syndrome (ARDS) as a result of viral infection caused by the SARS-Cov2 pathogen (COVID-19). Whilst DMX-200 has not yet been tested in the respiratory setting, it has an extensive safety database with a low AE profile unlike many immune modulators.

2. INTRODUCTION

DMX-200 (repagermanium) is a CCR2 inhibitor in clinical development that, when administered concurrently with an ARB, is designed to inhibit recruitment of monocytes implicated in the inflammatory cytokine environment of respiratory distress. Intervention in this inflammatory process may benefit in the treatment of moderate to severe ARDS in patients with suspected or proven COVID-19 infection.

An alternative crystal packing of repagermanium is named propagermanium. The structures of propagermanium and repagermanium are identical when in solution, and both have been available as a nutritional and dietary supplements since the 1970s in Japan and in other countries including the United States and Australia since the 1980s. (Kaplan B 2004)

Propagermanium has been available in Japan as a drug substance in the prescription product Serocion® since 1994. Drug doses up to 240 mg per day were studied during clinical development of Serocion®, and a 10 mg immediate release formulation administered 3 times daily (30 mg daily) was approved for the treatment of chronic hepatitis B infection. (The Pharma Letter 1994) Evidence for the clinical safety of propagermanium was submitted to the Japanese PMDA in support of the registration of Serocion® and has also been the subject of a number of investigator led studies.

The rationale for the adjunct therapy of repagermanium as an antagonist of CCR2, and an antagonist of AT1R, is the fundamental understanding that these receptors form functional dimer complexes on the cell surface that alter the pharmacology of each receptor. (Ayoub 2015) When these complexes are present, there is signalling cross-talk between receptors and the activation G-protein recruitment required for receptor signalling cannot be eliminated unless both receptors are antagonised simultaneously. (Ayoub 2015) Both CCR2 and AT1R have been independently implicated in the progression of a range of inflammatory diseases including chronic kidney disease, with CCR2 required for recruitment of inflammatory monocytes to the kidney, and AT1R antagonism shown to be renoprotective in proteinuric kidney disease (Metcalfe 2007) (Ota T 2002) (Lewis E 2001). Based on these anti inflammatory effects, Dimerix is currently developing DMX-200 (repagermanium) as an oral formulation for the treatment of chronic diseases where inflammatory-mediated processes are the driving factor in disease progression: DKD, FSGS, and ARDS related to COVID-19.

2.1 Use in ARDS and COVID-19

No group has yet had the capacity to test CCR2 inhibition in patients with respiratory complications of COVID-19, and most CCR2 inhibition programs have generally been associated with chronic inflammatory diseases. However, in cells such as activated monocytes where chemotaxis to areas of inflammation is driven by a cline of monocyte chemoattractant protein-1 (MCP-1) concentration being generated by the lung epithelium in response to viral damage, inhibition of CCR2 alone or in addition to AT1R, is predicted to inhibit this chemotaxis. In the models of inflammatory renal disease that Dimerix has studied and presented in Ayoub et al there is a decreased infiltration of monocytes to the damaged kidney, and decreased the subsequent fibrosis when treated with the combination of an ARB and a CCR2 inhibitor. (Ayoub 2015)

With regard to the lung epithelium itself, there is evidence that the AT1R receptor is expressed on lung epithelium and is implicated in inflammatory response (Wong 2012) While there is extensive evidence that the lung epithelium expresses MCP-1 in response to inflammatory challenge (Pechovsky 2005), less is known about the expression of CCR2 expression on the epithelium or

the alveoli. There is indeed some evidence that CCR2 is expressed on murine alveoli (Christensen 2004) but the co-expression of AT1R and CCR2 on the epithelium is unclear.

Given that CCR2 inhibition is central in a range of inflammatory diseases, the use of DMX-200 involving this mechanism is considered to be an appropriate intervention for patients with ARDS resulting from COVID-19. Whilst DMX-200 has not yet been tested in the respiratory setting, it has an extensive safety database with a low adverse event profile unlike many immune modulators and a significant rationale to support the use of DMX-200 in the treatment of community acquired pneumonia (CAP) and ARDS in patients with COVID-19.

2.1.1 CCR2 and AT1R in Cytokine Driven Inflammatory COVID-19

Literature suggests that in cases of COVID-19 there is an increase in the ligand of CCR2 called MCP-1 (or C-C motif chemokine ligand 2 [CCL2]). (Huang C 2020) Huang et al. reported that initial plasma interleukin 1 beta (IL-1B), interleukin-1 receptor antagonist (IL-1RA), IL-7 (interleukin 7), IL-8 (interleukin 8), IL-9 (interleukin 9), IL-10 (interleukin 10), basic fibroblast growth factor (FGF), GCSF (granulocyte colony stimulating factor), granulocyte macrophage colony stimulating fact (GMCSF), interferon (IFN), interferon gamma induced protein 10 (IP-10), MCP-1, macrophage inflammatory protein 1A (MIP-1A), macrophage inflammatory protein 1B (MIP-1B), platelet derived growth factor (PDGF), tumor necrosis factor (TNF), and vascular endothelial growth factor (VEGF) concentrations were higher in both intensive care unit (ICU) patients and non-ICU patients than in healthy adults; For MCP-1: ICU care > healthy control (p = 0.0032); No ICU care > healthy control (p = 0.0071)). Further comparison between ICU and non-ICU patients showed that plasma concentrations of IL-2 (interleuken 2), IL-7, IL-10, GCSF, IP-10, MCP-1, MIP-1A, and TNF were higher in ICU patients than non-ICU patients; For MCP-1: ICU care > No ICU care (p = 0.011)).

Additionally, Huang et al. noted that patients infected with 2019-nCoV also had high amounts of IL-1B, Interferon gamma (IFN-γ), IP-10, and MCP-1, probably leading to activated T-helper-1 (Th1) cell responses. (Huang C 2020) Moreover, patients requiring ICU admission had higher concentrations of GCSF, IP-10, MCP-1, MIP-1A, and TNFα than those not requiring ICU admission, suggesting that the cytokine and chemokine storm was associated with disease severity.

Xiong et al. (2020) found cytokines IL-10, CCL2/MCP-1, chemokine C-X-C motif ligand 10 (CXCL10)/IP-10, C-C motif chemokine ligand 3 (CCL3)/MIP-1A, and C-C motif chemokine ligand 4 (CCL4)/MIP-1B are highly expressed in COVID-19 patients' bronchoalveolar lavage fluid (BALF) samples. (Xiong Y 2020) Indeed, consistently in their study, Xiong et al. found the expression of a large number of cytokines and chemokines were significantly elevated in COVID-19 patients BALF samples compared to control, including pro-inflammatory cytokines chemokine C-X-C motif ligand 1 (CXCL1), chemokine C-X-C motif ligand 2 (CXCL2), chemokine C-X-C motif ligand 6 (CXCL6), chemokine C-X-C motif ligand 8 (CXCL8), CXCL10/IP-10, CCL2/MCP-1, CCL3/MIP-1A and CCL4/MIP-1B. Increased transcription of respective chemokine receptors such as CCR2 (CCL2/MCP-1 receptor) and CCR5 (CCL3/MIP-1A receptor) was also observed, indicating the activation of these inflammatory signalling pathways.

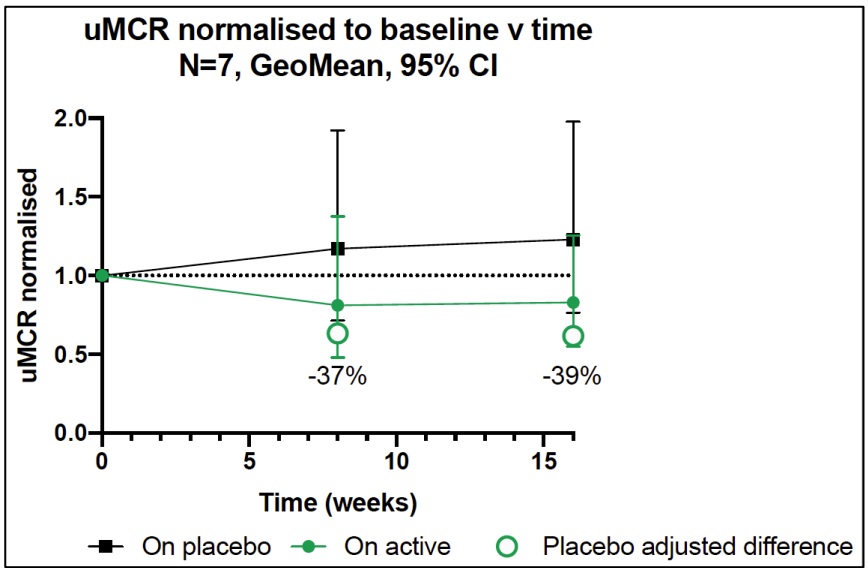
This relationship between increased the MCP-1 response to infection in pandemic coronavirus infections was also present in the 2003 Severe Acute Respiratory Syndrome (SARS) coronoavirus pandemic. In 2004 Wong et al. reported that pulmonary inflammation and extensive lung damage was observed in SARS patients and was associated with increased amounts of proinflammatory cytokines in serum (eg, IL-1B, IL-6, IL-12, IFN-γ, IP-10, and MCP-1. (Wong CK 2004)

Prior to the current pandemic of COVID-19, MCP-1 had been linked to severity of inflammatory response to ventilator-assisted pneumonia (VAP). (Huang C 2020) Plasma MCP-1 levels were reported as being significantly increased in the acute stage in VAP patients (1579.72 ± 211.47 ng/mL) when compared with patients without VAP (632.86 ± 349.91 ng/mL; $p = 0.0006$) and the control group (176.02 ± 10.11 ng/mL; $p < 0.0001$). Plasma MCP-1 levels remarkably decreased after treatment (1027.09 ± 183.25 ng/mL; $p = 0.0082$). Furthermore, there was also significant difference between non-VAP subjects and healthy controls ($p = 0.0007$). Plasma MCP-1 levels were significantly increased even in the remission stage of VAP patients when compared with non-VAP subjects ($p = 0.0149$) and healthy controls ($p < 0.0001$)."

Plasma MCP-1 levels were significantly increased in VAP patients who developed ARDS (1954.15 ± 294.81 ng/mL) when compared with patients without ARDS (1151.80 ± 269.73 ng/mL; $p = 0.0417$), healthy controls (176.02 ± 10.11 ng/mL; $p < 0.0001$), and non-VAP subjects (632.86 ± 349.91 ng/mL; $p = 0.0004$). Moreover, there was a significant difference between non-VAP subjects and healthy controls ($p = 0.0007$). Plasma MCP-1 levels were significantly increased in VAP subjects without ARDS compared with non-VAP subjects ($p = 0.0156$) and healthy controls ($p < 0.0001$)."

Recently, Dimerix has assessed the role of DMX-200 on urinary MCP-1 during clinical study DMX-200-202 which examined the safety and efficacy of DMX-200 in FSGS. Data presented in **Figure 1** show that when adjusted for urinary creatinine concentration, treatment with DMX-200 reduced the urinary MCR-1 to creatinine ratio (uMCR) in patients compared to when patients were treated with placebo. This treatment effect was an 37% compared to placebo after 8 weeks treatment and 39% after 16 weeks of treatment with DMX-200 compared to placebo.

Figure 1 Effects of DMX-200 on uMCR (as compared to placebo)



This relationship will be investigated in further clinical studies, and provides evidence for the potential benefit of DMX-200 in patients with ARDs where a reduction in MCP-1 concentrations would likely have clinical benefit.

2.1.1.1 Renin Angiotensin Aldosterone System (RAAS) Inhibition

Recent publications suggest that RAAS inhibition may be beneficial for COVID-19 patients based on the understanding of how coronaviruses such as SARS-associated coronavirus (SARS-CoV) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) bind to the angiotensin converting enzyme 2 (ACE2) receptor of the lung epithelium.

A review of the literature for SARS-CoV identified in 2003, reveals not only the identification of ACE2 as the binding partner of this family of viruses, but also the likely mechanism by which it results in acute severe lung injury. (Huang C 2020) The data provide a molecular explanation for the severe lung failure and lethality associated with SARS and it was hypothesized that that infections with SARS-CoV result in ACE2 downregulation through binding of SARS-CoV Spike protein to ACE2. Given that ACE2 is a key negative regulatory factor for severity of lung edema via the bradykinin-mediated mechanisms and acute lung failure, SARS-CoV Spike protein–mediated ACE2 downregulation then contributes to the severity of lung pathologies. This scenario would explain how this family member of the 'relatively harmless' coronaviruses has turned into a lethal virus.

Further, while there is no evidence yet with regard to the importance of AT1R specific to the immune response to SARS-CoV2, AT1R has been implicated in animal models of the adaptive immune response to other pathogens such as *Plasmodium* where AT1R activation promotes upregulation of interleukin-2 receptor α chain (IL-2Rα) and IL-2 production in CD8+ T-cells. Genetic ablation and use of the ARB losartan was shown to impair priming of *Plasmodium*-specific $CD8^+$ T cells as observed by reduced expression of activation markers such as CD69, CD160, and CD44, and decreased cytokine production and degranulation by *Plasmodium*-specific $CD8^+$ T cells. (Silva-Filho 2017)

A detailed summary of the literature and pathophysiology of COVID-19 with regard to RAAS blockade concluded that SARS-CoV-2 binding to ACE2 may attenuate residual ACE2 activity, further tipping the angiotensin converting enzyme (ACE)/ACE2 balance to a predominant ACE/ angiotensin II/ angiotensin II type 1 (AT1) axis signalling, in which AngII may then foster pulmonary vasoconstriction, and inflammatory and oxidative organ damage, ultimately progressing towards acute lung injury (ALI) and ARDS. (Sanchis-Gomar 2020)

It may be speculated that RAAS dysregulation may play a central role in the pathophysiology of COVID-19 associated ALI/ARDS, but definitive prospective, randomised, controlled studies are underway to address this issue.

To date, the best evidence for the importance of the RAAS system and RAAS blockade for the treatment of COVID-19 has come from retrospective studies of patients hospitalised in Wuhan and Hubei provinces, China.

A pre-print (Guan 2020) from a multi-centre team in Wuhan province conducted a retrospective review of 126 patients with existing hypertension who were being treated with an ACE inhibitor or ARB at the time of admission for COVID-19 with 125 age and sex-matched patients without hypertension. (Huang C 2020) While not significant, the authors found a much lower proportion of critical patients (9.3% vs 22.9%; p=0.061), and a lower death rate (4.7% vs 13.3%; p=0.216) were observed in ARBs/ACEIs group than non-ARBs/ACEIs group and concluded that the findings support the use of ARBs/ACEIs in COVID-19 patients with pre-existing hypertension. The ACE/ARB cohort also had lower inflammation markers (c-reactive protein and calcitonin) than the patient cohort with RAAS inhibition.

The most recent and largest retrospective study included data from Hubei province with 1128 adult patients with hypertension diagnosed with COVID-19, including 188 taking ACEI/ARB and 940 not taking an ACEI/ARB. (Huang C 2020) The unadjusted mortality rate was lower in the ACEI/ARB group versus the non-ACEI/ARB group (3.7% vs. 9.8%; P = 0.01). In a propensity score-matched analysis followed by adjusting imbalanced variables in mixed-effect Cox model, the results consistently demonstrated lower risk of COVID-19 mortality in patients who received ACEI/ARB versus those who did not receive ACEI/ARB (adjusted HR, 0.37; 95% CI, 0.15-0.89; P = 0.03). Further subgroup propensity score-matched analysis indicated that, compared to use of other antihypertensive drugs, ACEI/ARB was also associated with decreased mortality (adjusted HR, 0.30; 95%CI, 0.12-0.70; P = 0.01) in COVID-19 patients with hypertension.

Together, these data appear to support the use of RAAS inhibition in the treatment of COVID-19, and has lead to the initiation of several open-label and randomised controlled studies of RAAS inhibition in acute and sub-scute respiratory distress syndrome associated with COVID-19. (National Clinical Trials 2020)

Dimerix will continue to development of DMX-200 including inhibition of the RAS system simultaneously with inhibition of CCR2 as both treatments may have clinical benefit for patients with respiratory complications from COVID-19.

2.2 Selection of Dose

Dimerix proposes to use the investigational medicinal product (IMP) repagermanium at a daily dose of 240 mg. This dose will be delivered as 120 mg capsules taken on an empty stomach, twice a day, approximately 12 hours apart.

Non-clinical data in a subtotal nephrectomy (STNx) rat model of FSGS suggests that the combination of repagermanium and an ARB (irbesartan) was effective at human equivalent doses for repagermanium between 0.48 and 4.8mg/kg. Assuming an 80 kg human body weight, this translates to a daily dose of between 38.4 mg and 384 mg.

No evidence on the pharmacokinetic and pharmacodynamic relationship has been developed in animal models or clinical development of DMX-200 to treat ARDS.

A dose-escalation clinical study of repagermanium in renally-impaired patients (DMX-200-201) has shown no safety signals when the dose of repagermanium was escalated from 30 to 240 mg/day for a total duration of 28 weeks, with up to 12 weeks at the highest dose of 240 mg/day. Patients were on 75 to 300 mg irbesartan for the duration of this study. While not prospectively designed to test the efficacy of DMX-200, 27% patients achieved a partial response during treatment with response occurring at repagermanium doses ranging from 60 mg to 240 mg.

Detailed pharmacokinetic profiling of repagermanium in healthy volunteers was conducted in a Phase 1 study (DMX-200-101), with key pharmacokinetic data generated and this data used to make a quantitative pharmacometric model of repagermanium. This model incorporates variation in individuals expected in future studies including sex, age, body mass index, ethnicity, and renal impairment. Based on this modelling, Dimerix proposes to use the investigational medicinal product repagermanium at a daily dose of 240 mg during the planned clinical studies.

Further, based on nonclinical safety data, the daily dose of 240 mg is approximately 16-fold lower than the lowest no observed adverse effect level (NOAEL) observed in a 12-month, repeat-dose toxicity testing in dogs (human equivalent dose [HED] 3.84 g/day, (S. M. Miyazaki Y 1990) and

1333-fold lower than the lowest lethal dose, 50% (LD50) observed in dog (4,000 mg/kg) (S. M. Miyazaki Y 1990)

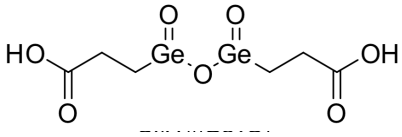
To date, Dimerix's preclinical in vivo pharmacology and clinical studies have been conducted using repagermanium as an adjunct to the ARB irbesartan (AVAPRO®, NDA 020757, Approved 30 Sept 1997). Irbesartan has been dosed at a maximum tolerated dose of 75, 150 and 300 mg in previous studies. Dimerix has confirmed that a range of other ARBs are also capable of inhibiting dimerisation of the AT1R/CCR2 heteromer to a similar extent as irbesartan, and recommend future clinical studies utilise ARBs dosed at "maximally tolerated dose (at least 50% of the maximum label dose) of irbesartan, losartan, valsartan, candesartan, olmesartan medoximil or azilsartan kamexomil" to have equal or higher inhibition of heteromeric signalling as irbesartan.

3. PHYSICAL, CHEMICAL AND PHARMACEUTICAL PROPERTIES AND FORMULATION

Repagermanium (DMX-200) is a hydrophilic small molecule and an organometallic compound of the element germanium. The compound was first synthesised in Japan in 1967.

The chemical and physical properties of repagermanium are presented in **Table 1**.

Table 1 Chemical and Physical Properties of Repagermanium

Name	Repagermanium
Synonyms	Propagermanium, organic germanium, proxigermanium, Ge-132, germanium sesquioxide, 2-carboxyethylgermasesquioxane, SK-818, bis(2-carboxyethylgermanium) sesquioxide
Structure	
Chemical Formula	$C_6H_{10}Ge_2O_7$
Molecular Weight	339.40 g/mol
CAS Number	12758-40-6
Physical Properties	White, odourless, microcrystalline powder

3.1 Repagermanium Drug Substance

Development of a current good manufacturing practice (cGMP) method of manufacture has been conducted by:

Patheon API Manufacturing
309 Delaware St,
Greenville, South Carolina 29605, USA
DUNS No. 962538372
FEI No. 3001451369

The facility has a current United States Food and Drug Administration (US FDA) establishment listing and has been successfully audited by other regulatory agencies. The facility has not yet had a requirement for accreditation with other regulatory agencies and has not sought registration outside of the US FDA.

Repagermanium drug substance is controlled by the drug substance manufacturer to the specification presented in **Table 2**.

Table 2 Repagermanium Drug Substance Specification

Test	Method	Acceptance Criteria
Appearance	Visual	White crystalline powder
Identification by HPLC	In house	Retention time conforms to chromatogram of reference standard
Identification by FT-IR	USP	Conforms to reference spectrum
Repagermanium content (Titration)	In-house	97.0 – 103.0% w/w
Repagermanium content (HPLC)	In-house	98.0 – 102.0% w/w
Germanium content (ICP-MS)	In-house	38.0 – 48.0% w/w
Germanium dioxide content (GC-MS)	In-house	NMT 500 ppm
Acrylic acid (HPLC)	In-house	NMT 1500 ppm
Water Content (Karl Fischer)	USP < 921>	NMT 1.0% w/w
Solid State Form (XRPD)	In-house	Conforms to reference diffractogram for repagermanium
Elemental impurities (ICP-MS)	USP <233>	As NMT 1.5ppm Cd NMT 0.5ppm Hg NMT 3ppm Pb NMT 0.5ppm Co NMT 5ppm V NMT 10ppm Ni NMT 20ppm
Microbial Limit Test	USP <61> & <62>	TVAC: < 10^3 cfu/g TYMC: < 10^2 cfu/g E. coli: absent in 1g

NLT = Not less than; NMT = Not More than; w/w = weight/weight; a/a = area/area; ppm = part per million; cfu = colony forming units; HPLC = High Performance Liquid Chromatography; XRPD = X-Ray Powder Diffraction; FTIR = Fourier Transform Infrared; ICP-MS = Inductively Coupled Plasma Mass Spectrometry; USP = United States Pharmacopeia.

3.2 DMX-200 Drug Product

DMX-200 capsules is an immediate release capsule for oral administration. The product is described as: A size 2 white opaque capsule containing free flowing white powder.

The empty hard gelatin capsule is a commercially available product sourced from Capsugel. The unit formula is presented in **Table 3** below.

Table 3 Unit Formula – DMX 200 Capsules

Ingredient	Function	Quality Standard	Quantity (mg) per capsule
Repagermanium	Active substance	In house	120.0 mg
Lactose monohydrate	Filler	USP/NF	117.6 mg
Magnesium Stearate	Lubricant	USP/NF	2.4 mg
Capsule Fill Weight			240.0 mg
Size 2 Opaque Gelatin Capsule			61.0 mg
Gelatin (bovine and/or porcine)	Structure	USP/NF, Ph. Eur.	qs 100%
Titanium Dioxide (E171)	Opacifier	USP/NF	2.9079%
TOTAL WEIGHT			301.0 mg

Notes: NF = National Formulary; USP = United States Pharmacopeia; Ph. Eur. = European Pharmacopeia; qs = quantity sufficient; mg = milligram

The drug product will be manufactured by:

Patheon Pharmaceuticals Inc
2110 East Galbraith Road
Cincinnati
Ohio 45237
US

FEI: 1510437
DUNS: 005286822

The capsules are manufactured using standard manufacturing techniques in accordance with cGMP and are controlled in accordance with the specification presented in **Table 4**.

Table 4 DMX-200 Capsules Specification

Test	Method	Specification Limits
Appearance	In house	Size 2 opaque capsules containing free flowing white powder
Identification by FTIR	USP < 197>	Conforms to reference
Identification by HPLC	In house	HPLC retention time corresponds to reference standard
Assay (HPLC)	In House	90.0 – 110.0 % Label Claim
Related Substances	In house	Record results
Disintegration	USP<701>	NMT 5 minutes
Germanium Dioxide	In House	NMT 50 ppm
Water Content	USP<921>	Record results
Uniformity of Dosage Units (Weight variation)	USP <905>	Where N = 10, Acceptance value ≤ 15% (L1) Where N = 30, Acceptance Value ≤ 15% and no individual unit is 75% ≤ X ≤ 125%
Microbial Content	USP< 61>/ USP< 62>	TAMC NMT 10^3 cfu/g TYMC 10^2 cfu/g *E.coli* Absent in 1 g

Notes: NMT = Not More than; ppm = part per million; cfu = colony forming units; HPLC = High Performance Liquid Chromatography; FTIR = Fourier Transform Infrared; USP = United States Pharmacopeia.

3.3 Shelf Life

Stability data has been generated on a batch of DMX-200 capsules which has been stored at long term and accelerated conditions for up to 12 months. These data are considered to support a shelf life of the finished product of 12 months when stored at 15 - 25°C.

4. NONCLINICAL STUDIES

4.1 Introduction

As an established drug substance, the preclinical safety of repagermanium has been studied extensively over the last 30 years. Evidence of the nonclinical effects of repagermanium reported here have been obtained through independent investigation by Dimerix, publicly available literature, including summary information supporting the registration of the Serocion® drug product by the Japanese PMDA. A summary of all available data is presented in **Table 5**.

Table 5 Summary of Nonclinical Data

ICH Requirement	Source	GLP Compliance Status	Study Description
Pharmacology (ICH S7A)			
In Vitro Pharmacology	Literature (Ayoub 2015)	Non-GLP	Target identification and validation of AT1R and CCR2 heteromer in HEK293 cells.
In Vivo Combination Pharmacology	Dimerix Study	Non-GLP	Rat FSGS model – 3 mg/kg repagermanium by oral gavage concurrently with 10 mg/kg irbesartan
	Dimerix Study	Non-GLP	Rat FSGS model – 30 mg/kg repagermanium by oral gavage concurrently with 10 mg/kg irbesartan
	Dimerix Study	Non-GLP	Rat FSGS model – 100 mg/kg repagermanium by oral gavage concurrently with 10 mg/kg irbesartan
Toxicokinetics (ICH S3A)			
Pharmacokinetics	Dimerix Study	Non-GLP	Single dose of 30 mg/kg of repagermanium by oral gavage in rats
Pharmacokinetics	Dimerix Study	Non-GLP	Single dose of 30 mg of repagermanium orally in cynomolgus monkeys
	Dimerix Study	Non-GLP	Single dose of 30 mg/kg of repagermanium by oral gavage in FSGS rat model
	Literature (Miyao, et al. 1980)	Non-GLP	Single dose of ^{14}C-labelled propagermanium by oral and intravenous routes in rats
In Vivo Metabolism	Literature (Miyao, et al. 1980)	Non-GLP	Single dose of 25 mg/kg of ^{14}C-labelled propagermanium orally in rats
	Literature (Sanwa, Kagaku and Kenkyusho 2010)	Non-GLP	Single doses of 1.0 mg/kg or 100 mg/kg of propagermanium orally in rats
General Toxicology (ICH M3)			
Acute Toxicity - Rodents	Literature (Kanda, et al. 1990)	Non-GLP	Doses of up to 9953 mg/kg of propagermanium orally in mice
	Literature (Kanda, et al. 1990)	Non-GLP	Doses of up to 12500 mg/kg of propagermanium orally in rats
	Literature (Lalla, Shah and E 2010)	GLP	Doses of up to 5000 mg/kg of propagermanium orally in rats

ICH Requirement	Source	GLP Compliance Status	Study Description
Acute Toxicity – Non-Rodents	Literature (Miyazaki, Acute toxicity test of Proxigermanium (SK-818) in dogs 1990)	Non-GLP	Doses of up to 4000 mg/kg of propagermanium orally in dogs
Single Dose Toxicity - Rodents	Literature (Kanda, et al. 1990)	Non-GLP	Doses of up to 1000 mg/kg of propagermanium orally in rats
Subacute Toxicity – Non-Rodents	Literature (Miyazaki, Segawa and Kano, et al. 1990)	Non-GLP	Doses of up to 2000 mg/kg of propagermanium orally in dogs
Toxicokinetics - Rodents	Literature (Anger, et al. 1992)	Non-GLP	Dose of 1 g/kg orally in rats assessed over 6 months
Chronic Toxicity - Rodents	Literature (Nakagawa, Segawa and Kano 1990)	Non-GLP	Doses of up 750 mg/kg orally in rats assessed over 1 year
Chronic Toxicity-Non-Rodents	Literature (Miyazaki, Segawa and Kano, et al. 1990)	Non-GLP	Doses of up to 80 mg/kg orally in dogs assessed over 1 year
Chronic Toxicity – Rodents	Literature (Reddeman, 2020)	GLP	Doses of up to 2000 mg/kg orally in rats assessed over 90-days
Carcinogenicity (ICH S1B)			
2-Year Rodent Carcinogenicity Study	Literature (Doi, Imai and al 2017)	Non-GLP	CB6F1-Tg rasH2 Mice
2-Year Rodent Carcinogenicity Study	Literature (Iwadate and Yamaguchi 2018)	Non-GLP	F344 Rats
Genotoxicity (ICH S2B)			
In Vitro Mutagenicity (Ames)	Literature (Sato, et al. 1990)	Non-GLP	*E.Coli* Wp2 HCr and *S.typhimurium*
In Vitro Chromosomal Damage	Literature (Sato, et al. 1990)	Non-GLP	Don strain cells
In Vivo Genotoxicity	Literature (Sato, et al. 1990)	Non-GLP	Mice Micronucleus

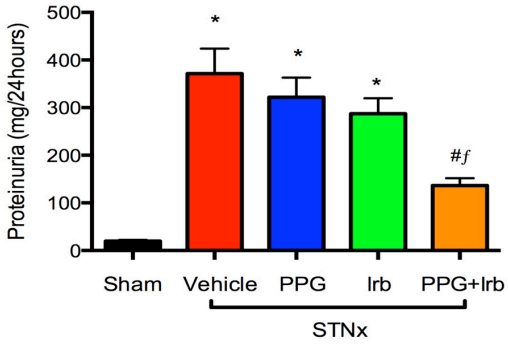
ICH Requirement	Source	GLP Compliance Status	Study Description
	Literature (Reddeman, 2020)	GLP	In Vitro Reverse Mutation Assay
	Literature (Reddeman, 2020)	GLP	In Vitro Mammalian Aberration Assay
	Literature (Reddeman, 2020)	GLP	In Vivo Mammalian Bone Marrow Erythrocyte Micronucleus Assays
Reproductive and Developmental Toxicity (ICH S5)			
Embryo-Foetal Development	Literature (Hayasaka, et al. 1990)	Non-GLP	Rat/Wistar
Peri- and Postnatal Development	Literature (Sato, et al. 1990)	Non-GLP	Rat

Abbreviations: CYP = Cytochrome P450; FSGS = focal segmental glomerulosclerosis: GLP = good laboratory practice; hERG = human Ether-à-go-go-Related Gene; ICH = International Conference on Harmonisation; PPB = plasma protein binding

4.2 Nonclinical Pharmacology

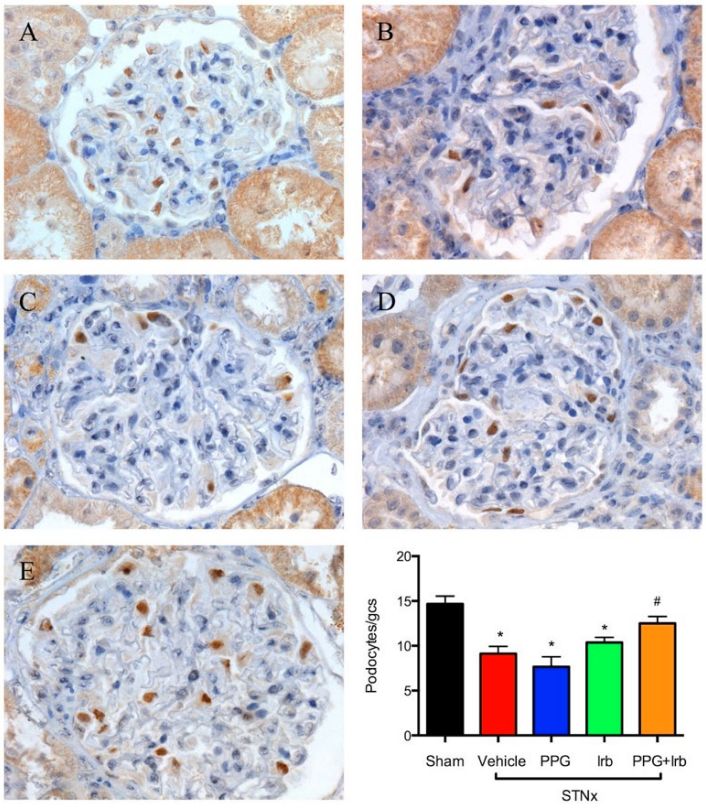
Dimerix has identified an interaction between AT1R and CCR2 in vitro in HEK293 cells in the proprietary Receptor-HIT assay and confirmed that simultaneous inhibition of both receptors in vivo reduces proteinuria and increases podocyte numbers in a rat STNx model (Ayoub 2015). The results in the STNx model demonstrate that the combination of repagermanium and irbesartan, compared to the individual use of either drug, show a reduction in proteinuria (**Figure 2**) and podocyte loss (**Figure 3**)

Figure 2 Combined Therapy Significantly Reduces Proteinuria Compared to Repagermanium or Irbesartan Alone



Notes: Sham - control rat, no disease, Vehicle - STNx rat, no treatment, PPG - repagermanium 30 mg/kg, once daily by gavage, Irb - irbesartan 10 mg/kg/day in drinking water. PPG+Irb - repagermanium and irbesartan, same doses as monotherapy. Presented as geometric means ± SD. * P<0.05 v sham, # P<0.01 v STNx, *f* P<0.05 vs Irb.

Figure 3 Combined Therapy Shows Significantly Better Podocyte Pathology Versus Untreated Animals



Notes:

(A) Sham - control rat, no disease.
(B) Vehicle - STNx rat, no treatment.
(C) PPG - repagermanium 30mg/kg, once daily by gavage.
(D) Irb - irbesartan 10mg/kg/day in drinking water.
(E) PPG+Irb - repagermanium and irbesartan, same doses as monotherapy.

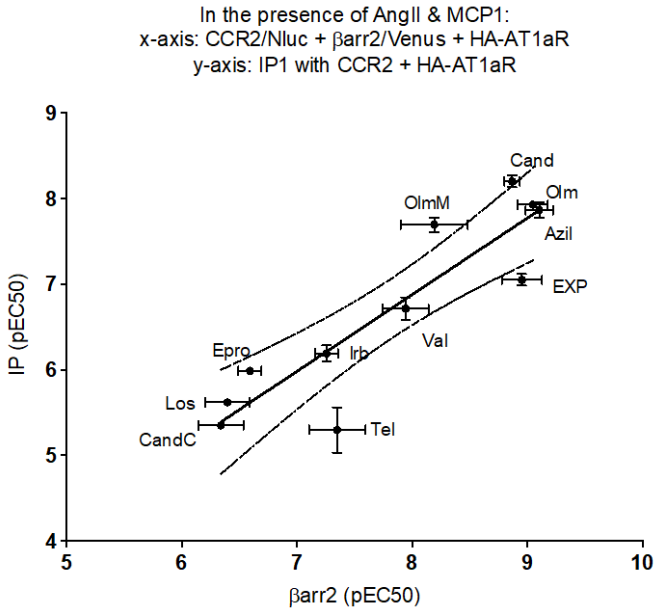
Presented as geometric means ± tolerance factors (mg/24 hours). Representative photomicrographs of WT-1 (podocytes) immunostaining in glomerular cross sections (gcs, above) and the podocytes counting per gcs (below). In comparison with sham rats (A), STNx rats (B) were associated with a significant reduction in the number of podocytes. Treatment of STNx rats with irbesartan in combination with PPG (E) was associated with less podocyte loss, while treatment with either PPG (C) or IRB (D) alone did not attenuate podocyte loss. Magnification x400. * P<0.05 v sham, # P<0.05 v vehicle treated STNx.

4.2.1 Use of DMX-200 as an Adjunct to Angiotensin Receptor Blockers

To date, Dimerix's preclinical in vivo pharmacology and clinical studies have been conducted using repagermanium and the ARB irbesartan. Irbesartan was selected for use in the development of DMX-200 as a treatment for DKD as it had significant inhibition of the AT1R/CCR2 heteromer and it is approved for the "treatment of diabetic nephropathy in hypertensive patients with type 2 diabetes, an elevated serum creatinine, and proteinuria" (AVAPRO, 2018).

As there is most likely a wide range of specific ARBs used to treat FSGS, DMX-200 capsules may be used in patients receiving a stable dose of a range of different ARBs. To support this strategy, Dimerix has conducted a range of in vitro pharmacology assessments of signalling of the AT1R/CCR2 heteromer in the presence of different ARBs. Cell-based experiments were conducted as per (Ayoub 2015) but included a range of ARBs to determine which compounds had equal or higher AT1R/CCR2 signalling inhibition as irbesartan used in the nonclinical and clinical studies conducted to date. Data in **Figure 4** present the inhibition of heteromer signalling following inhibition of AT1R with candesartan and its metabolite candesartan cilexetil, losartan and it's metabolite EXP3174, telmisartan, irbesartan, neprosartan, losartan and its metabolite EXP3174, valsartan, olmesartan medoxomil, and azilsartan kamedoxomil.

Figure 4 Inhibition of Heteromer by ARBs as determined by Inhibition of Downstream Inositol Phospholipid Signaling and Recruitment of β-arrestin 2



Notes:
XY scatter plot of inhibition of inositol phospholipid signalling versus recruitment of β-arrestin 2 by different ARBs. (pEC50) is the -log10 transformed EC50 of IP signalling measured using an IP assay, mean of 3 experiments. Barr2 (pEC50) is the -log10 transformed EC50 of βarr2 coupling BRET using Receptor-HIT, mean of 6 experiments. CandC is candesartan cilexetil. Los is losartan. Tel is telmisartan. Irb is irbesartan. Epro is eprosartan. EXP is EXP3174 the metabolite of losartan. Val is valsartan. Olm is Olmesartan medoximil. OlmM is the metabolite of olmasartan. Azil is azilsartan kamedoxomil. Cand is candesartan. Error bars on each data point are standard error of the mean (SEM). Trend line is linear regression with 95% confidence interval (CI).

The data presented in **Figure 4** shows that there is consistently high inhibition of downstream signalling of the AT1R/CCR2 heteromer, as exhibited by reduced inositol phospholipid signalling and recruitment of the heteromer with β-arrestin 2 and Gi, with the ARBs: irbesartan, valsartan, candesartan, olmesartan medoximil, and azilsartan medoxomil.

In order to assess the potential for drug-drug interactions and the potential for a negative safety profile beyond what has been observed in the DMX-200 nonclinical and clinical program with repagermanium and irbesartan to date, a table of characteristics of each ARB that may potentially influence an interaction with repagermanium has been compiled and is presented in **Table 6.**

Table 6 Characterisation of ARB Drugs

	Repagermanium	Irbesartan	Losartan	Valsartan	Candesartan	Olmesartan medoximil	Azilsartan kamedoxomil
Year First Approved by FDA	-	1997	1995	1996	1998	2007	2011
Indications	Proposed: FSGS	Hypertension, diabetic nephropathy	Hypertension, diabetic nephropathy	Hypertension, heart failure	Hypertension, heart failure	Hypertension	Hypertension
Active Metabolite	No	No	Yes	No	Yes - prodrug	Yes - prodrug	Yes - prodrug
Bioavailability (%)	30	70	33	25	42	26	60
Food Effect	Not	No	Not significant	Yes	No	No	No
P450 Metabolism	-	CYP 2C9	CYP 2C9 and 3A4	Unknown CYP	-	No	CYP 2C9
$t_{1/2}$ - Drug (hrs)	3.5	11 - 15	2	9	3.5 - 4	13	11
$t_{1/2}$ - Metab (hrs)	-		6 - 9		3 - 11		
PPB – Drug (%)	UNK	90 - 95	98.7	95	99.5	>99	99
PPB - Metab (%)	-		99.8				
Renal Elimination (%)	6.5%	20	35	13	33	35 - 50	42
Hepatic Elimination (%)	-	80	60	83	67	50 - 65	55
Known Drug Transporters	UNK	OATP1B1, OATP1B3	OAT1, OAT3, URAT1	OAT1, OAT3	OAT1, OAT3, URAT1	OATP1B1, OATP1B3 URAT1	-
Known Drug Interactions	UNK. None identified to date	Drugs that raise K, lithium, NSAIDS, Cox-2 inhibitors.	Rifampicin, fluconazole, drugs that raise K, lithium, NSAIDS, Cox-2 inhibitors.	Drugs that raise K, lithium, NSAIDS, Cox-2 inhibitors.	Drugs that raise K, lithium, NSAIDS, Cox-2 inhibitors.	Drugs that raise K, lithium, NSAIDS, Cox-2 inhibitors, colesevelam hydrochloride.	Drugs that raise K, lithium, NSAIDS, Cox-2 inhibitors.
Dose Mod. in Hepatic Impairment	None	No change in dose	↓ initial dose	No change in dose	↓ initial dose	No change in dose	No change in dose
Dose in Renal Impairment	None	No change in dose	No change in dose	No change in dose	No change in dose	No change in dose	No change in dose

	Repagermanium	Irbesartan	Losartan	Valsartan	Candesartan	Olmesartan medoximil	Azilsartan kamedoxomil
Off Target Cellular Effects (* not at therapeutic dose)	UNK	↑PPARγ,* ↓↓TxA2/PGH2, ↓cell growth	↓↓URAT1, ↑PPARγ,* ↓TxA2/PGH2	-	PPARγ,*	-	↑PPARγ gene expression
AT1 Receptor Binding	None	Insurmountable	Surmountable	Insurmountable	Insurmountable	Insurmountable	Insurmountable

Abbreviations: AT1 = angiotensin II type 1; CYP = Cytochrome P450; FDA = food and drug administration; FSGS = focal segmental glomerulosclerosis; GLP = good laboratory practice; hrs = hours; ICH = international conference on harmonisation; NSAID = non-steroidal anti-inflammatories; PPB = plasma protein binding; t ½ = biological half life; UNK = unknown

Notes:

Data sourced from current FDA labels, (Munger 2011) (Chapy, et al. 2015) and (Yamada, et al. 2007) and current DMX-200 studies.

As presented in **Table 6,** the safety profiles of irbesartan, losartan, valsartan, cadesartan, olmesartan and azilsartan kamedoximil are well characterised with few known drug interactions. Known drug interactions with all ARBs include the negative effect with drugs that increase potassium, lithium, non-steroidal anti-inflammatories, and Cox-2 inhibitors. Losartan is also known to have an interaction with rifampicin and fluconazole, and olmesartan medoximil with colesevelam hydrochloride.

There is no known metabolism of repagermanium in rats, where there are no metabolic transformations of 3-[(2-carboxyethyl-oxogermyl)oxy-oxogermyl]propanoic acid. (Sanwa, Kagaku and Kenkyusho 2010).

Given this lack of metabolism or observed induction or inhibition of Cytochrome P450 or substrates, it is unlikely that there will be any drug-drug interactions observed between repagermanium and irbesartan, losartan, valsartan, cadesartan, olmesartan and azilsartan kamexomil and these ARBs are recommended for use with repagermanium.

4.3 Pharmacokinetics and Product Metabolism in Animals

Dimerix has completed 2 non-good laboratory practice (non-GLP) pharmacokinetic studies of repagermanium in male rats and male cynomolgus monkeys:

- Rat study - analysis of the relative plasma levels after administration of a single-dose of repagermanium by gavage of 30 mg/kg dissolved in water. Following administration to N=10 rats, there was an increase of repagermanium in blood plasma over the first 4 hours followed by a rapid drop-off by 8 hours post treatment, and < 5% of peak amount remaining at 24 hours post treatment. Individual pharmacokinetic parameters were not determined.
- Cynomolgus monkey study - single oral administration of 30 mg immediate release and extended release repagermanium formulations in fasting, non-naïve male cynomolgus monkeys. The study was a cross-over design where each animal (N=6) received both formulations. The mean maximum plasma concentration (Cmax) of the immediate release formulation in plasma was 0.33 mg/mL with time to maximum plasma concentration (tmax) at 2.33 hours and biological half life (t1/2) of 6.59 hours, and Cmax of the extended release formulation was 0.17 mg/mL with tmax at 5.00 hours with a t1/2 of 9.34 hours.

Evidence for the pharmacokinetics of repagermanium in animals presented in the literature includes:

- A non-GLP pharmacokinetic study in rats, performed with 14C-labelled propagermanium administered in a single-dose by oral and intravenous routes. After intravenous dosing, radioactivity disappeared rapidly from the blood. Oral bioavailability was reported to be about 30%, with all absorbed compound being excreted in the urine within 72 hours as unchanged drug. No metabolites were detected. Tissue distribution data showed even distribution of radioactivity between blood and tissues, with no preferential distribution or accumulation in any tissue and low transfer across the blood-brain barrier. Pharmacokinetic parameters and clearance rate from tissue and faeces was not determined (Miyao, et al. 1980).
- A non-GLP pharmacokinetic study in rats of single doses of 1.0 mg/kg or 100 mg/kg of propagermanium orally was performed. Propagermanium was not metabolised when administered to rats, did not induce enzymes involved in metabolism including cytochrome

P450 isoenzymes in vitro, and all unchanged propagermanium was excreted in the urine and faeces. (Sanwa, Kagaku and Kenkyusho 2010).

4.4 Toxicology

Toxicology data for propagermanium has been obtained from literature reviews, and repeat dose toxicology data of propagermanium and irbesartan is currently underway.

Propagermanium has been demonstrated to be of low acute oral toxicity, with published oral LD50 values of:

- 7050 mg/kg in rats (Kanda, et al. 1990).
- 5600 mg/kg in mice (Kanda, et al. 1990).
- > 4000 mg/kg in dogs (Miyazaki 1990).

4.4.1 Repeat-Dose Toxicology Studies

The toxicity of propagermanium has been well documented in many repeat-dose toxicity studies. These are summarised in **Table 7.**

Table 7 Summary of Published Repeat-Dose Studies of Propagermanium

Study (Reference)	Duration	Route	Dose	Species	Findings
Acute toxicity (Kanda, et al. 1990)	3 weeks	Oral	0, 4000, 4800, 5760, 6912, 8924, 9953 mg/kg (Ge-132)	Mice	LD50 5600 mg/kg in males, 5800 mg/kg in females
			0, 6000, 7200, 8640, 10400, 12500 mg/kg (Ge-132)	Rats	LD50 7700 mg/kg in males, 7050 mg/kg in females
		Intraperitoneal	0, 1000, 1200, 1440, 1728, 2074, 2488 mg/kg	Mice	LD50 1250 mg/kg in males, 1300 mg/kg in females
			0, 1000, 1200, 1440, 1728, 2074, 2488 mg/kg (Ge-132)	Rats	LD50 1750 mg/kg in males, 1670 mg/kg in females
		Intravenous	0, 200, 3000 (dissolved in 10% $NaHCO_2$) mg/kg (Ge-132)	Mice	LD50 not calculated as there were no deaths even at maximum possible dose
			0, 200, 3000 (dissolved in 10% $NaHCO_2$) mg/kg (Ge-132)	Rats	LD50 not calculated as there were no deaths even at maximum possible dose
		Subcutaneous	0, 4000 mg/kg (Ge-132)	Mice	LD50 not calculated as there were no deaths even at maximum possible dose
			0, 4000 mg/kg (Ge-132)	Rats	LD50 not calculated as there were no deaths even at maximum possible dose
Acute toxicity (Miyazaki, Segawa and Kano, et al. 1990)	3 weeks	Oral	0, 2000, 4000 mg/kg (SK-818)	Dogs	No deaths were observed. Vomiting was observed in 2 of 3 animals to which 2000 mg/kg was administered and all 3 animals to which 4000 mg/kg was administered 30 minutes to 2 hours after administration. In addition, a slight decrease in weight was observed in these animals the day after administration. No noteworthy abnormalities were subsequently observed.
Acute toxicity – GLP (Lalla, Shah and E 2010)	2 weeks	Oral	0, 2000, 5000 mg/kg OxyPowder® (Equiv 40 mg/kg/day Ge-132)	Rats	Compound exhibited high degree of safety even at dose level of 5000 mg/kg body weight of OxyPowder® (Equiv 40 mg/kg/day Ge-132)

Study (Reference)	Duration	Route	Dose	Species	Findings
Subacute toxicity (Miyazaki, Segawa and Kano, et al. 1990)	3 months	Oral	320, 800 and 2000 mg/kg (SK-818)	Dogs	No observed effect level < 320 mg/kg. Lethal toxic dose considered to be 800 mg/kg, the dosage at which tissue damage to the digestive tract, vomiting and the like were observed.
Subchronic oral toxicity (Anger, et al. 1992)	6 months	Oral	1g/kg (Ge-132)	Rats	No particular toxic symptoms, and no behaviour problems except a small decrease of body weight in male rats were observed. A significant decrease of erythropoiesis and some significant changes in leucocyte ratios were demonstrated. The main marked effect was a moderate renal dysfunction characterised by a tubular disease with the presence of cylinders, swelling of tubules cells and flocculus deposits.
Toxicokinetic (Anger, et al. 1992)	6 months	Oral	1g/kg (Ge-132)	Rats	Toxicokinetic studies showed that germanium urinary excretion was constant and linked to the received dose. Six months later, no preferential accumulation in organs was evident.
Chronic toxicity (Nakagawa, Segawa and Kano 1990)	1 year	Oral	83, 250 and 750 mg/kg (SK-818)	Rats	Dosage of 83 mg/kg produced no effects. At 750 mg/kg, increased water intake, loose stools and diarrhoea, and death were observed, and this is likely to constitute a lethal toxic dose. The dosage of 250 mg/kg, meanwhile, resulted in dilatation of the caecum in a few rats but this change was reversible and did not result in any histopathological damage. This dosage therefore did not correspond to a no observed effect dosage, but it was not concluded to be a toxic dose.
Chronic toxicity (Miyazaki, Segawa and Kano, et al. 1990)	1 year	Oral	89, 267 and 800 mg/kg (SK-818)	Dogs	No observed effect level 89 mg/kg. 800 mg/kg should be considered a lethal toxic dose as vomiting often occurred in this group.
Toxicity (Miyao, et al. 1980)	6 months	Oral	Rats - 30, 300 and 3000 mg/kg Dogs – 125, 259 and 500 mg/kg (Ge-132)	Rats and dogs	There were no substantial differences between the control and experimental groups in body weight curves. At all the dose levels no toxic effects or abnormalities were observed in laboratory, clinical and pathological examinations.
Toxicity – GLP (Lalla, Shah and E 2010)	28 days	Oral	0, 250, 500, 1000 mg/kg OxyPowder® (Equiv 8mg/kg/day (Ge-132)	Rats	No observed effect level was 1000 mg/kg for both male and female animals. Equivalent 8 mg/kg/day Ge-132.

Study (Reference)	Duration	Route	Dose	Species	Findings
Comparison of influence of propagermanium and GeO_2 on renal lesions in rats (Asano, et al. 1994)	8 weeks	Oral	480 & 2400 ppm Ge-132 in drinking water; 300 & 1500 ppm GeO_2 in drinking water	Rats with chemically induced renal lesions	Both renal impaired and normal rats experienced vacuolisation and deposits of PAS-positive material after treatment with GeO_2. Ge-132 administration was not associated with any alteration in the changes induced by adriamycin or mercuric chloride. It was concluded that the high dose of propagermanium was without adverse effects in the kidneys in which glomerular or proximal tubular dysfunction was present. This suggests that this compound does not exert renal toxicity, even when given at a high dosage to renal injured rats, which further indicates that it would not exacerbate renal dysfunction already present.
Toxicity (Sanai, et al. 1991)	24 weeks	Oral	75 mg/kg $Ge0_2$, 120 mg/kg of Ge-132, or no germanium.	Rats	Increased blood urea nitrogen and serum phosphate as well as decreased creatinine clearance, weight loss, anaemia and liver dysfunction were apparent at week 24 only in the GeO_2 treated group. Vacuolar degeneration and granular depositions were evident in the degenerated renal distal tubes in the rats of this group. Neither toxic nor renal histological abnormalities were manifested in either Ge-132 or the control group. The renal tissue content of germanium was high at weeks 24 and 40 in the GeO_2 group. From these results, it is concluded that GeO_2 causes characteristic nephropathy while Ge-132 does not.
Toxicity GLP (Reddeman, 2020)	90-days	Oral	500, 1000, 2000 mg/kg bw/day of Ge-132	Rats	There were no mortalities in any group during the study period. In daily clinical observations, paler than normal stools were observed in male and female animals in the 1000 and 2000 mg/kg bw/day. There were no differences with respect to the controls in: behaviours or reactions to stimulation in functional observed behaviour testing, changes in overall body weight or weight gain, changes observed on opthalmologic examinations, histological findings, or organ weights. No target organs were identified.

Abbreviations: LD50= lethal dose, 50%; PAS = periodic acid Shiff's; mg = milligram; kg = kilogram; ppm = parts per million.

All HED calculations were conducted according to the US FDA Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical studies for Therapeutics in Adult Healthy Volunteers (2005) assuming a 60 kg adult.

Repeated dose administration of propagermanium shows no significant toxicology at doses relevant to human use.

The key findings from published repeat-dose studies presented in **Table 7** on propagermanium are:

- In a 3-month oral toxicity study in an undefined number of rats; effects on weight gain, water intake, and stool consistency were observed at higher dosages (doses administered ranged from 256 to 4000 mg/kg/day). No specific target organ toxicity was noted. All animals exhibited recovery or an improvement in symptoms 1-month after use was stopped. A NOAEL of 256 mg/kg/day was reported based on weight and stool consistency effects on at higher doses. This corresponded to a HED of 2.46 g/day (Sanwa, Kagaku and Kenkyusho 2010).
- In a 6-month oral toxicity study in groups of N=30 male and N=30 female rats; germanium was administered in an aqueous solution at 1 g/kg/day for 5 days per week (HED 9.6 g/day). Moderate renal lesions were identified in the male but not female rats at the end of the study, and no other organ damage noted. Toxicokinetic studies demonstrated urinary excretion of germanium increased progressively from the beginning to the end of the administration period and remained proportional to the administered dose. The germanium absorbed did not remain in the body and did not accumulate in preferential tissues with residual amounts of approximately 1.5 to 2.5 µg/g observed in all tissues (Anger, et al. 1992). The authors did not state a NOAEL.
- In a 3-month oral subacute toxicity study in groups of N=8 female and N=8 male dogs at dosages of zero (vehicle control) 320, 800 and 2000 mg/kg/day in an aqueous solution; diarrhoea, vomiting, slight weight loss, and increased water intake were observed at the higher dosages (800 and 2000 mg/kg/day). Excretion of loose stools, muddy stools and watery stools was observed in the lowest dose 320 mg/kg group. There were no notable findings in haematology and clinical chemistry investigations at any dose, and liver and renal function (dye clearance) tests were normal in all animals. Histopathological examination revealed epithelial desquamation in the stomach and erosions/haemorrhage in the ileum for some dogs at 800 or 2000 mg/kg/day. The NOAEL was stated to be lower than the lowest 320 mg/kg/day used in this study due to the gastrointestinal effects at the lowest dose (HED of 9.75 g/day) (Miyazaki, Segawa, et al. 1990).
- In a 12-month oral toxicity study in groups of N=40 male and N=40 female rats at dosages of zero (vehicle control) 83, 250 and 750 mg/kg/day, urinalysis revealed a decreased pH in the 250 and 750 mg/kg/day groups. During the administration period, loose stools or watery diarrhoea were frequently observed in males and females in the 750 mg/kg/day group, and water intake also increased in these groups. In addition, although necropsy suggested a relationship between enlargement of the caecum and the loose stools and diarrhoea, no tissue damage was observed in the intestines and the symptoms disappeared upon withdrawal of the drug after 2 months. During the administration period, 1 death was observed in a female in the 750 mg/kg who exhibited piloerection, loose stools, abdominal

distension and emaciation from the middle of the administration period and continuous watery diarrhoea for several days prior to death on day 287 of administration. There were no notable findings in haematology and clinical chemistry investigations. Kidney weights were increased in males at 750 mg/kg/day and caecum weights were increased in rats of both sexes at 250 and 750 mg/kg/day. Histopathological examination revealed increased tubule regeneration in the kidneys and foamy cells in the lung alveolar spaces in males at 750 mg/kg/day. A NOAEL was noted at 83 mg/kg/day (HED 0.84 g/day) due to the increased kidney weight in groups administered higher doses (Nakagawa, Segawa and Kano 1990).

- In a 12-month oral toxicity study in groups of N=8 male and N=8 female dogs per group at dosages of zero (vehicle control), 89, 267 and 800 mg/kg/day, diarrhoea, vomiting, and slight weight loss were observed at higher dosages (267 and 800 mg/kg/day). There were no notable findings in haematology, blood gas and clinical chemistry investigations, and liver and renal function (dye clearance) tests were normal in all animals. Organ weights were unaffected by treatment allocation. There were no treatment-related changes at histopathological examination. The NOAEL was 89 mg/kg/day (HED 2.88 g/day) due to the gastrointestinal symptoms at higher doses (Miyazaki, Segawa, et al. 1990).

- In a 90-day GLP oral toxicity study conducted per OECD test guidance 408, groups of N=10 male and N=10 female Han:WIST rats per group at dosages of zero (vehicle control), 500, 1000 and 2000 mg/kg/day, there were no observed changes in body weight or weight gain, ophthalmic examination, functional observed behaviours, food consumption, hematology or clinical chemistry, gross pathology, organ weights, and histological examination. There were no notable findings between control and test groups, and no dose-related effects observed in any findings between test groups. The no-observed-adverse-effect level (NOAEL) was determined to be 2000 mg/kg bw/day.

4.4.2 Reproductive Toxicology

Details of published nonclinical studies investigating the reproductive toxicity of propagermanium are summarised in **Table 8.**

Table 8 Summary of Reproductive Toxicology

Study (Reference)	Duration	Route	Dose (Ge-132 or SK818)	Species	Key Findings
Embryo-foetal (Hayasaka, et al. 1990)	Day 0 gestation-12 weeks post-birth	Oral	1000, 2000, 4000 mg/kg/day on Days 7 to 17 of gestation (SK-818)	Rats	Maternal toxicity was observed at 2000 and 4000 mg/kg/day, but there were no effects of litter parameters. Offspring of treated dams that were allowed to litter showed normal growth and development through weaning and up to 12 weeks of age.
Perinatal and postnatal	6 weeks	Oral	750, 1500 and 3000 mg/kg	Rats	Decreased birth weight was observed in males and females in the 3000 mg/kg administration group. No effect was

Study (Reference)	Duration	Route	Dose (Ge-132 or SK818)	Species	Key Findings
(Sato, et al. 1990)			(SK-818)		observed on offspring during the postnatal period in terms of general growth and differentiation, development of sensory function and reproductive organ differentiation after weaning. In addition, no effect was observed on emotionality, motor coordination, learning ability and reproductive potential. The no observed effect level (NOEL) approximately 750 mg/kg in dams, 1500 mg/kg in offspring.

The key findings from published studies of the reproductive toxicity of propagermanium include:

- Embryo-foetal toxicity studies were conducted in groups of N=23 female rats. Dosages of zero (vehicle control), 1000, 2000 and 4000 mg/kg/day were administered in aqueous solution via gavage on Days 7 to 17 of gestation. Maternal toxicity was observed at 2000 and 4000 mg/kg/day where 5 animals died, and 5 animals became moribund in the 4000 mg/kg administration group. In addition, 1 animal in the 2000 mg/kg administration group died as a result of an administration error and early miscarriage occurred in 1 animal in the 4000 mg/kg administration group. There were no effects on litter parameters between the control or treatment groups including development state at birth, death rate, general condition and external appearance at birth, organ weights, necropsy findings, postnatal differentiation. However, there was a significant difference in terms of latency in the 4000 mg/kg/day group in an open field behavioural test, but no effect between groups of offspring was observed in a water maze test. No effect on the reproductive capacity of the offspring was observed between treatment groups. The NOAEL was deemed to be 1000 mg/kg for dams due to increased death rate at higher doses, and 2000 mg/kg for live foetus's due to the significant difference in the open field test of the 4000 mg/kg/day litter group (HED of 4.8 and 9.6/day) (Hayasaka, et al. 1990).
- A peri/post-natal toxicity study was conducted in groups of N=22 to 24 rats at dosages of zero (vehicle control), 750, 1500 and 3000 mg/kg/day propagermanium, administered in an aqueous solution via gavage from Day 17 of gestation to Day 21 post-partum. There was a transient decrease in food intake in dams administered 1500 mg/kg the day after initial administration, and a decrease in the 3000 mg/kg administration group throughout the administration period during gestation. Suppression of weight gain in dams was observed during gestation in the group of dams administered 3000 mg/kg. In the offspring, decreased birth weight was observed in males and females from the 3000 mg/kg administration group. There was decreased weight observed throughout the postnatal period, but there was no difference in the final amount of weight gained during the postnatal period. No effect was observed in general growth and differentiation, development of sensory function and reproductive organ differentiation after weaning between treatment groups. In addition, no effect was observed on emotionality, motor coordination, learning ability and reproductive potential between groups. The no observed effect level (NOEL) was noted as 750 mg/kg in dams due to the changes in food intake at

higher doses, and 1500 mg/kg in offspring due to the changes in birth weight at higher doses (HED 7.2 and 14.4 g/day, respectively) (Sato, et al. 1990).

No reproductive toxicity has been observed for propagermanium at clinically-relevant doses, with the lowest reproductive toxicity NOAEL observed at a HED of 4.8 g/day for a 60 kg adult, which is ~20X greater than the dose to be administered in the proposed clinical study.

4.4.3 Carcinogenicity Studies

The potential for carcinogenicity as a result of treatment with repagermanium has been the subject of a number of nonclinical studies which are reported in published literature.

The carcinogenicity of repagermanium was studied following dietary administration of 0, 0.3, 0.8 and 2.5% of repagermanium to CB6F1-Tg rasH2 mice (20 M/F/group) for 26-weeks (Doi, Imai and al 2017). As a positive control, 10 rasH2 mice of each sex received a single IP injection of 75 mg/kg N-methyl-N-nitrosourea (MNU). There was no difference in survival between repagermanium treated mice and control group mice. At the end of the study, the survival rates of mice fed 0, 0.3, 0.8 and 2.5% repagermanium were 100, 95, 100 and 90%, respectively, for males and 100, 100, 100 and 90%, respectively for females. Loose stools, increased water intake, and dilatation of cecum were evident at 2.5% repagermanium in the diet, however, these were not associated with any histopathological changes in the cecum of these mice. There was no significant increase in incidence of any neoplastic lesions compared to negative controls.

Toxicokinetic analysis was conducted in mice (12 M/F per group) and blood samples collected from 3 M/F per group at week 4 and 26 (at two time points, 11.00 am and 3.00 pm). Toxicokinetic data showed that plasma concentration of repagermanium increased with increase in dietary concentrations of repagermanium after week 4 and week 26 in male and female mice. The plasma concentration of propagermanium was in the same range at both toxicokinetic time points. There was a tendency for repagermanium concentration in the morning to be higher than the one in the afternoon. Plasma repagermanium concentrations are presented in **Table 9**.

Table 9 Plasma Repagermanium Concentration in Mice Following Dietary Administration for 4 and 26 Week

Table 6. Plasma Ge-132 concentration in rasH2 mice fed a diet containing Ge-132 for 4 and 26 weeks.

Sex	Dose	Plasma concentration (μg/mL)							
		4 weeks				26 weeks			
		11:00		15:00		11:00		15:00	
		No. of animals	Mean concentration	No. of animals	Mean concentration	No. of animals	Mean concentration	No. of animals	Mean concentration
Male	0.3% Ge-132	3	2.27	3	1.11	3	1.64	3	1.40
	0.8% Ge-132	3	6.04	3	3.31	3	4.00	3	3.03
	2.5% Ge-132	3	12.9	3	8.63	3	10.6	3	10.5
Female	0.3% Ge-132	3	1.81	3	1.36	3	1.53	3	1.26
	0.8% Ge-132	3	5.87	3	3.00	3	4.07	3	2.43
	2.5% Ge-132	3	14.9	3	12.4	3	13.0	3	11.6

Overall, repagermanium was not carcinogenic at doses up to 3.837 g/kg/day (2.5% in diet) in male mice and 5.442 g/kg/day (2.5% in diet) in female mice. The HEDs were calculated as 312 mg/kg

in males and 442.4 mg/kg in females and were 78 to 110-fold higher than the proposed clinical dose of 240 mg/day for repagermanium.

For male and female mice, 3.837 g/kg/day and 5.442 g/kg/day, respectively, provided an average systemic exposure to repagermanium (Cp bound plus unbound at 4 weeks, 11 am) about 16 and 18 times, respectively, the average systemic exposure in humans (about 0.814 µg/mL) receiving the maximum recommended daily dose of 240 mg/day (120 mg BID). This is based on the assumption that single 120 mg/kg oral dose in humans gives Cmax of 0.814 µg/mL and there is no accumulation of drug after administration of the second oral dose of 120 mg. Although a total daily dose is 240 mg, it is anticipated that Cmax for repagermanium will not exceed 0.814 µg/mL. Another study investigated the carcinogenicity of repagermanium following dietary administration of 0, 0.6, 1.3 and 2.5% of repagermanium to F344 rats (20 M/F/group) for 2 years (Iwadate and Yamaguchi 2018). The study reported that dietary supplementation with repagermanium at 1.3% (585 mg/kg/day, HED 94.35 mg/kg) for males and 2.5% (1509 mg/kg/day) for females were carcinogenic based on increased incidences of benign or malignant pheochromocytomas of the adrenal. No other neoplastic lesions were induced up to 2.5% repagermanium in both sexes. Development of pheochromocytomas in rats was attributed to impairment in calcium/phosphorus homeostasis caused by repagermanium. However, it was stated that the mechanism by which repagermanium induces pheochromocytomas of the adrenals in the rats is not relevant to humans. Therefore, adrenal medullary tumour development as a result of long term repagermanium ingestion in rats was considered to be not relevant for human risk assessment.

There was no significant difference in mortality between controls and treated animals during the course of the study. At the end of the study, the survival rates of rats fed 0, 0.6, 1.3 and 2.5% propagermanium were 54, 74, 66 and 64%, respectively, for males and 74, 74, 64 and 70%, respectively for females.

Toxicokinetic analysis was conducted in rats (3-5 M/F per group) at week 2, 5 and 30. Toxicokinetic data showed that plasma concentration of repagermanium increased with increase in dietary concentrations of repagermanium as presented in **Table 10.**

Table 10 Toxicokinetic Data for Repagermanium Following Dietary Administration of 0.6, 1.3 and 2.5% of Repagermanium to Rats in a 2 Year Study

Toxicokinetic Parameter	0.6% Repagermanium		1.3% Repagermanium		2.5% Repagermanium	
	Week 2					
	Male	Female	Male	Female	Male	Female
Mean plasma concentration (µg/mL)	3.77	7.04	15.91	16.48	18.0	23.59
AUC 0-24 (µg.hr/mL)	86.4	86	173.7	143.3	221.7	301.1
	Week 5					
Mean plasma concentration (µg/mL)	7.41	3.97	19.44	9.68	46.47	8.89
	Week 30					
Mean plasma concentration (µg/mL)	6.56	3.35	15.72	11.46	40.40	16.66

Overall, a non-carcinogenic dose for repagermanium in rat was 265 mg/kg/day (HED 42.74 mg/kg/day) for males (0.6% repagermanium in diet) and 746 mg/kg/day (HED 120.3 mg/kg/day) for females (1.3% repagermanium in diet). The HED were 10 to 30-fold higher than the proposed clinical dose of 240 mg/day for repagermanium assuming a human body weight of 60 kg.

For male and female rats, 265 mg/kg/day and 746 mg/kg/day, respectively, provided an average systemic exposure to repagermanium (AUC 0-24 bound plus unbound) about 16 and 28 times, respectively, the average systemic exposure in humans (about 5.298 µg/h/mL) receiving the maximum recommended daily dose of 240 mg/day (120 mg BID). This is based on the assumption that single 120 mg/kg oral dose in humans gives AUC 0-last of 5.298 µg/h/mL and there is no accumulation of drug after administration of the second oral dose of 120 mg. Although a total daily dose is 240 mg, it is anticipated that AUC 0-last for repagermanium will not exceed 5.298 µg/h/mL.

For carcinogenicity studies, the existing literature provides sufficient evidence regarding the carcinogenicity potential of repagermanium in GLP studies and at doses that are higher than the proposed clinical doses.

4.4.4 Genotoxicity Studies

A detailed review of all available and pre-published literature relating to the genotoxicity of repagermanium has been commissioned and reviewed by a registered toxicologist. This includes a recent series of GLP genotoxicity studies conducted by a manufacturer of repagermanium, Designed Nutritional Products (Orem, Utah).

In summary, review of the genetic toxicity package reviewed indicated the following:

- Repagermanium was non-mutagenic in two independent in vitro bacterial reverse mutation assays, performed to GLP (Reddeman, 2020) and non GLP (Suto, et al. 1990) and conducted with *Salmonella typhimurium* and *Escherichia coli* up to 5000 µg/plate in presence and absence of metabolic activation (S9 mixture).
- In another in vitro non-GLP study, repagermanium (5-30 µg/mL) was described as an anti-mutagen, markedly reducing the number of revertant mutants induced by10 kRad of gamma-rays in B/r WP2 Trp *Escherichia coli* (Mochizuki and Kada 1982).
- Repagermanium was negative in the in vitro mammalian chromosome aberration assay (GLP) conducted with Chinese Hamster Lung (CHL) V79 cells at up to 2000 µg/mL in presence and absence of metabolic activation (S9 mixture). The top concentration of 2000 µg/mL was selected based on the preliminary cytotoxicity test (Reddeman, 2020)
- In an independent non-GLP in vitro mammalian chromosome aberration assay conducted with Don cells derived from CHL cells, a significant increase in the number of cells with chromosomal aberrations was reported with statistical significance at the highest dose of 20 mg/mL in presence and absence of metabolic activation (S9 mixture) (Suto, et al. 1990). It is noted the concentrations selected in this study (5 to 20 mg/mL) all exceed the top

recommended concentration of 0.5 mg/mL and 1 mM as per International Council on Harmonization (ICH) S2(R1) guidelines for genotoxicity studies.

- Repagermanium was negative in two independent in vivo mammalian bone marrow erythrocyte micronucleus assays (GLP and non GLP) conducted in the mouse at doses up to 2000 mg/kg (Reddeman, 2020) and 5600 mg/kg (Suto, et al. 1990) respectively, administered by the oral route.

Overall, the package of in vitro and in vivo studies performed to GLP provide evidence that repagermanium does not have mutagenic, clastogenic, or in vivo genotoxic potential under the applied test systems up to the maximum recommended test concentrations or the limiting dose. The studies conducted by Redemann et al present adequate robust information and are in line with the ICH S2(R1) requirements for genotoxicity testing and data interpretation for pharmaceuticals for human use (ICH 2013). The in vitro positive results seen only at very high test concentrations in Don cells, reported by Suto et al was not reproduced in a GLP in vitro study in CHL cells, nor was there any positive results in the Ames test or the in vivo mouse micronucleus assays tested to limit concentrations/doses specified in guidance documents.

Key findings from published studies are summarized in **Table 11** as follows:

Table 11 Summary of Genotoxicity Studies of Repagermanium

Study	Test strains	Dose Levels (µg/plate)	Test System and Exposure	Findings
Non-GLP Mutagenicity – reverse mutation test SK- 818 (Suto, et al. 1990)	E.coli Wp2 Hcr and S.typhimurium TA 1535, TA100, TA1537, TA1538 and TA98.	Up to 5,000 µg/plate	Agar plate, vehicle or positive control in the presence and absence of S9- mix. 37ºC for 2-3 days.	No increase in revertant colony count and no correlation with concentration at any concentration including the high concentration (5,000 µg/plate), irrespective of bacterial strain or metabolic activation

Study	Test strains	Dose Levels (µg/plate)	Test System and Exposure	Findings
Non-GLP Mutagenicity – chromosomal aberration test (Suto, et al. 1990)	Don strain cells	Up to 20 mg/mL (SK-818)	Cell proliferation inhibition test by the colony formation method, treated with 5 mL of 20.0, 17.5, 15.0, 12.5, 10.0, 7.5 and 5.0 mg/mL for 6hrs.	Increase in the number of cells with chromosomal aberrations in the high concentration (20 mg/mL) treatment group at the limit of solubility 12 hr after treatment in the absence of S9 mix and 18 hr after treatment in the presence of S9 mix. In addition, an increase in endoreduplication was observed 18 hr after treatment.
Non-GLP Mutagenicity – micronucleus test (Suto, et al. 1990)	10 week old Slc:ddY strain male mice	Doses of 5,600 mg/kg, 2,800 and 1,400 mg/kg, administered orally (SK-818)	30 hrs treatment Number of erythrocytes with micronuclei were calculated from bone marrow. The ratio of orthochromatic erythrocytes and polychromatic erythrocytes was recorded.	Tendency toward reduction in the ratio of polychromatic erythrocytes to orthochromatic erythrocytes in the high dose administration group at the maximum tolerated dose, but no increase in the number of cells with micronuclei was observed in any administration group
Non-GP Reverse Mutation Assay (Mochizuki and Kada 1982)	*Escherichia coli* B/r WP2 Trp	5, 10, 15, 20 and 30 µg/mL	The bacterial mutations were studied using: 1) mutagenic assay in soft agar 2) liquid-phase antimutagenic assay and 3) reconstruction experiment in Escherichia coli B/r WP2 Trp.	Repargermanium was shown to be non-mutagenic, markedly reducing the number of revertant mutants induced by 10kRad of gamma rays in B/r WP2 Trp *Escherichia coli*

Study	Test strains	Dose Levels (µg/plate)	Test System and Exposure	Findings
GLP Reverse Mutation Assay (Reddeman, 2020)	*Escherichia coli* and *S.typhimurium*	16, 50, 160, 500, 1600, and 5000 µg/plate	Initial range-finding and confirmatory assays were performed using the plate incorporation procedure and pre-incubation method, respectively, with S typhimurium strains TA1535, TA1537, TA98, and TA100 and E coli strain WP2(uvrA) in both the presence and absence of a metabolic activation mixture S9.	No test article-related background inhibition or increases (reversion rate ≥ 2 for S. typhimurium TA98 and/or TA100 and/or E. coli WP2 uvrA and reversion rate ≥ 3 for S. typhimurium TA1535 and/or TA1537, compared to vehicle control) in the number of revertant colonies were seen for any of the strains at any concentration level, either in the presence or absence of the metabolic activation in the initial or confirmatory mutation tests.

Overall, these data are considered to indicate negative genotoxicity potential, for repagermanium either acting directly or indirectly on DNA.

5. EFFECTS IN HUMANS

5.1 Introduction

Propagermanium has been available as a drug substance in the prescription product Serocion® in Japan since 1994 where a 10 mg immediate release formulation administered 3 times daily (TID) (30 mg daily) is approved for the treatment of chronic hepatitis B infection. (The Pharma Letter 1994) At least 32,700 patients have been treated with Serocion® as of 2003. (Hirayama, Suzuki, et al. 2003)

Repagermanium has also been available as a nutritional or dietary supplement since the 1970s in Japan and in other countries including the United States (US) and Australia since the 1980s. (Kaplan, et al. 2004) However, there is little published evidence of the safety or efficacy of repagermanium use in this context.

Several investigator-led clinical studies using propagermanium (not as Serocion®) have been published, including:

- Hepatitis B: double blind, placebo-controlled studies in 182 biopsy proven chronic hepatitis B patients – repagermanium administered at 30 mg per day for 16-week duration – 101 patients received repagermanium. (Hirayama, Suzuki, et al. 2003) The study drug was reported to be generally well tolerated and the only AEs reported more commonly than placebo were 2 cases of eosinophilia. No laboratory findings of severe immune response or renal injury were reported.
- Myeloma: open-label study of propagermanium efficacy in 10 patients with multiple myeloma. Doses were 10 to 40 mg daily over 1 to 12 months duration. (Tsutsumi, et al. 2004) Depression was reported as a possible AE in a single patient.
- Type 2 diabetes and nephropathy: an open-label, parallel two-arm pilot trial of 30 mg propagermanium daily for 12-months in 29 patients with type 2 diabetes and nephropathy with macroalbuminuria > 30 mg/g and estimate glomerular filtration rate > 30 mL/min/1.73 m^2. The treatment was generally well tolerated, with no significant effect on renal function at the end of the treatment period (Hara, et al., 2020).

Dimerix has also sponsored a number of clinical studies of repagermanium to support the use of DMX-200 in the treatment of CKDs. Details of these studies are summarised in **Table 12** below.

Table 12 Summary of Clinical Studies Conducted on DMX-200

Study Number	Study Title	Population	Status
DMX-200-101	A phase I pharmacokinetic study investigating the administration of repagermanium in immediate release capsules and extended release capsules.	N=15 healthy volunteers	Complete
DMX-200-201	A phase 2a study investigating the safety and efficacy of DMX-200 capsules (increasing doses from 30-240 mg/day for a total period of 28 weeks).	N=27 patients with CKD	Complete

Study Number	Study Title	Population	Status
DMX-200-202	A phase 2a, double blinded, randomised, placebo controlled crossover study evaluating the safety and efficacy of repagermanium in patients with FSGS who are receiving irbesartan	N=8 patients with FSGS	Complete
DMX-200-203	A Phase 2, double blinded, randomised, placebo controlled, crossover study evaluating the safety and efficacy of repagermanum in patients with diabetic kidney disease who are receiving irbesartan	N=45 patients with diabetic kidney disease	Complete

Abbreviations: CKD=chronic kidney disease; FSGS = focal glomuleral segmentation.

All Dimerix studies have been conducted using a daily dose of up 240 mg DMX-200. The Phase 1 study in healthy volunteers (DMX-200-101) delivered a single 120 mg dose of DMX-200. The Phase 2a study in patients with CKDs (DMX-200-201) delivered up to 80 mg of DMX-200 TID for a total daily dose of 240 mg. The Phase 2a study in patients with FSGS (DMX-200-202) and the Phase 2 study in patients with DKD (DMX-200-203) delivered two doses of 120 mg DMX-200 for a total daily dose of 240 mg.

DMX-200 has also been provided for compassionate use in Australia since 2017 under the Australian Therapeutic Goods Administration Special Access Scheme, with some patients with renal disease receiving continuous treatment for over 4 years.

5.2 Pharmacokinetics and Product Metabolism in Humans

The pharmacokinetic profile for DMX-200 has been established based on literature data and the outcome of clinical studies conducted by Dimerix.

5.2.1 Dimerix Study DMX-200-101

Objectives: The primary objectives of the study were to determine and compare the pharmacokinetic profiles and relative bioavailability of a single oral dose of a capsule (immediate release formulation) and tablet (extended release formulation) of DMX-200. Another primary objective was to also identify if there was a food effect on the pharmacokinetic profile and relative bioavailability of the tablet (extended release formulation) of DMX-200.

Methods: The study was a single-centre, randomised, open-label, 2-way crossover, single-dose study with 3 treatment periods conducted in healthy participants. A total of 15 participants were enrolled into 2 cohorts (Cohort A and Cohort B).

Participants in Cohort A were randomised to receive:

- Dose 1: 120 mg capsule formulation (4 × 30 capsules) while fasting;
- Dose 2: 120 mg tablet formulation (4 × 30 tablets) while fasting;
- Dose 3: 120 mg tablet formulation (4 × 30 tablets) after a meal.

Participants in Cohort B were randomised to receive:

- Dose 1: 120 mg tablet formulation (4 × 30 tablets) while fasting;

- Dose 2: 120 mg capsule formulation (4 × 30 capsules) while fasting;
- Dose 3: 120 mg tablet formulation (4 × 30 tablets) after a meal.

No participant was a member of more than 1 cohort.

The population of participants were males or females aged between 18 and 50 years with a body mass index between 18.0 and 30.0 kg/m^2 who were generally healthy without any medical history expected to influence study findings. The study excluded participants who were regular smokers (more than 10/day), females who were pregnant or breast feeding or those determined to have abnormal clinical laboratory, physical examination or medical history findings at the screening visit.

Participants were screened from -14 days prior to dose administration. Participants were admitted to the clinical research unit on Day -1 and remained confined to the unit for 24 hours post-dose. On Day 1, participants were randomised and received Dose 1 and underwent extensive pharmacokinetic assessments until 30 hours post dose. On Days 7 and 14, participants returned to the unit and received Doses 2 and 3 on Days 8 and 15, respectively, completing necessary study procedures. Participants returned to the unit on Day 24 for a follow-up visit.

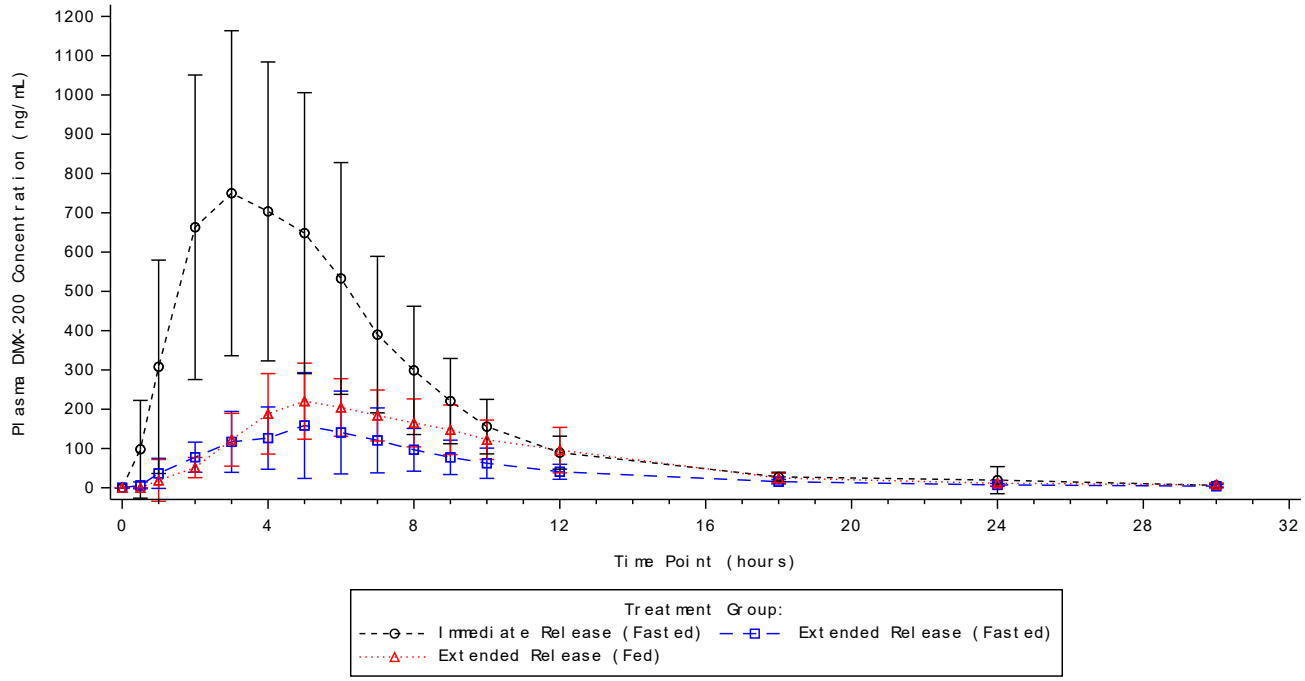
Study Results: During the study, 15 participants were randomised to treatment and completed the study as planned. In Cohort A (N=8): 7 (87.5%) males and 1 (12.5%) female was enrolled. In Cohort B (N=7): 4 (57.1%) males and 3 (42.9%) females were enrolled. The mean age and body mass index was similar between cohorts. The majority of participants were Caucasian in both cohorts. The pharmacokinetic population included all 15 participants administered IMP.

Plasma repagermanium concentration:

The following key findings were observed:

- Overall, mean plasma repagermanium concentration over time profiles showed an initial peak over 3 to 5 hours followed by a mono-exponential decline. While this profile was consistent across all 3 treatments, and comparable from the 18-hour time point onwards, the capsule (fasted) formulation peaked sooner and produced a mean maximum concentration that was approximately 3.5-fold and 4.5-fold higher than the tablet (fed) and tablet (fasted) formulations, respectively. (**Figure 5)**
- The mean Cmax was highest and earliest in the immediate release formulation (fasted) group, with a concentration of 749.8 ng/mL occurring at the 3-hour time point. Both extended release formulations reached a mean Cmax by the 5-hour time point, however, the tablet (fed) group recorded a higher mean maximum of 220.4 ng/mL compared to 158.4 ng/mL for the tablet (fasted) group. (**Figure 5**)

Figure 5 Mean Plasma Repagermanium Concentration (Linear) Following Single 120 mg dose of Immediate-Release Capsule and Extended Release Table formulations of DMX-200 (With and Without Food)



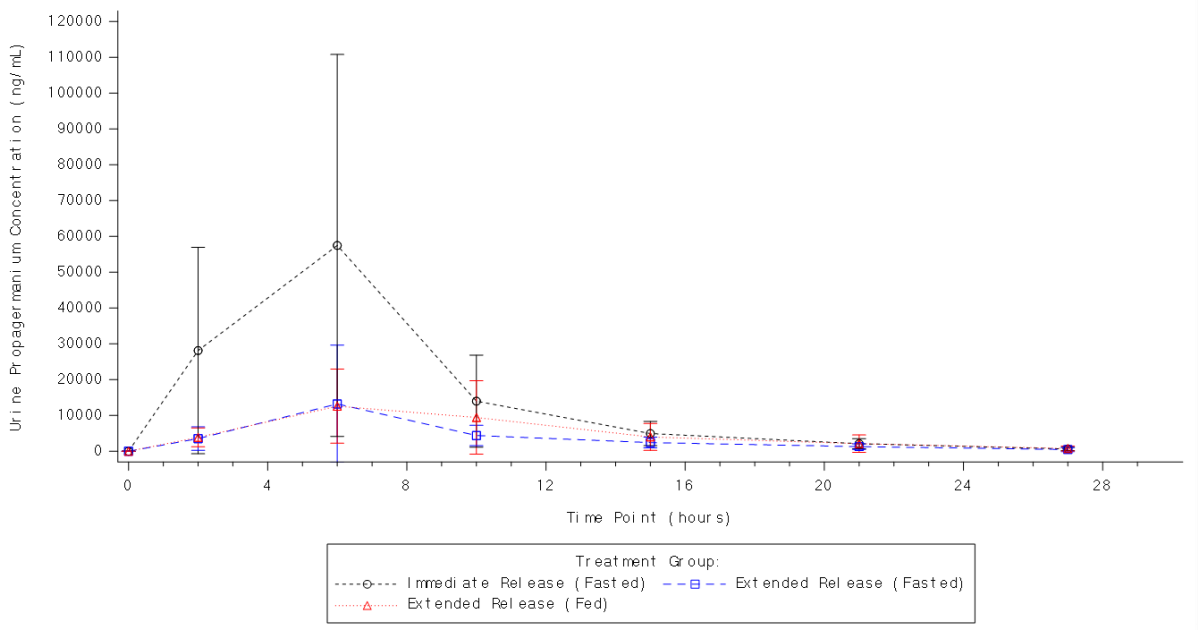
Footnote: For the calculation of summary statistics, values below limit of quantification were set to zero. The lower limit of quantification was 5 ng/mL. Mean values have been plotted at the mid-point of each time interval. Error bars indicate standard deviations

Urine repagermanium concentration:

The following key urine concentration findings were observed:

- Overall, mean repagermanium urine concentration over time profiles showed an initial peak during 4 to 8 hours post-dose followed by a mono exponential decline. While this profile was consistent across all 3 treatments, and comparable from 18 to 24 hours onwards, the capsule (immediate release, fasted) formulation produced a mean maximum concentration that was approximately 4.5-fold higher than the tablet (extended release, fasted) and tablet (extended release, fed) formulations. (**Figure 6**)

Figure 6 Mean Urine Repagermanium Concentration (Linear) Following Single 120 mg Dose of Immediate and Extended Release DMX-200 (With and Without Food)



Footnote: For the calculation of summary statistics, values below limit of quantification were set to zero. The lower limit of quantification was 20 ng/mL. Mean values have been plotted at the mid-point of each time interval. Error bars indicate standard deviations

Plasma Pharmacokinetic Parameters:

The following key plasma pharmacokinetic findings were observed:

- Mean Cmax and area under the curve from first timepoint to last timepoint (AUC(0-last)) were highest in the capsule (fasted) group (813.8 ng/mL and 5298 h/ng/mL respectively) and approximately 3-fold and 4-fold higher than those reported for the tablet (fed) and tablet (fasted) groups, respectively.
- Mean tmax was shortest for the capsule group (3.25 hours) and similar for the tablet formulation, regardless of fasted or fed conditions (4.43 hours and 5.63 hours, respectively).
- Mean t½ was also shortest in the capsule group (3.57 hours) but longest in the tablet (fasted) group (5.67 hours).
- The time delay observed in the tablet (fasted) group was approximately 3-fold higher than that observed in the capsule (fasted) group and approximately 11-fold higher in the tablet (fed) group compared with the capsule (fasted) group.
- The mean elimination rate constant was similar across all 3 groups.
- The apparent mean total body clearance and mean total volume of distribution was fastest and lowest in the capsule (fasted) group followed by the tablet (fed) group and the tablet (fasted) group.
- The relative bioavailability for the tablet formulation was reduced relative to the capsule formulation when both were administered under fasted conditions.

- Comparison of the tablet formulation administered after fed and fasted conditions identified a moderate food effect with bioavailability in the fed condition relative to the fasted condition.

Urine Pharmacokinetic Parameters:

The following key urine pharmacokinetic findings were observed:

- The percentage of dose recovered in urine over 30 hours post-dose was similar for the tablet preparations, with mean values of 6.56% and 9.66% for tablet (fasted) (7869.52 µg; n=14) and tablet (fed) (11596.07 µg; n=13), respectively.
- The mean values were approximately 2.5-fold higher in the capsule (fasted) preparation with 26.66% (31989.32 µg; n=13) of the dose recovered in urine.

Conclusions: Overall, the relative bioavailability for the tablet (extended release) formulation was reduced relative to the capsule formulation when both were administered under fasted conditions. Comparison of the tablet formation administered after fed and fasted conditions identified a moderate food effect with higher bioavailability in the fed condition relative to the fasted condition. Following analysis of this study, Dimerix has decided to continue development of the capsule (immediate release) formulation due to the poor bioavailability of DMX-200 when administered in the tablet formulation.

5.2.2 Published Pharmacokinetic Studies of Repagermanium

The pharmacokinetics of repagermanium in humans is also available in published literature. The pharmacokinetics of repagermanium in males has been reported (Miyao, et al. 1980) who compared oral and intravenous routes of administration. The doses used ranged from 25 to 75 mg/kg (total propagermanium doses of 1750 mg to 5350 mg assuming 70 kg body weight). Oral bioavailability was reported to be 30%. Half-life was not reported but urinary excretion was reported to be very rapid by all routes of administration and recovery within 9 hours was over 80%, suggesting low residual tissue levels.

Long, Zeng and Zhao (1996) reported human single-dose pharmacokinetic data obtained with oral administration of a liquid formulation of propagermanium (100 g/L) in 24 male and female volunteers (Long, Zeng and Zhao 1996). Propagermanium was administered at doses of 1, 2 and 4 gm/m^2 (for an administered dose range of 1.36 to 4.02 g). The tmax was reported to occur at 1.2 hours post-dose and elimination half-life was estimated between 4.0 to 6.9 hours. At the lower dose the elimination half-life was 5.2 ± 1.2 hours. There were no clear trends with increasing dose except for increasing Cmax and exposure (area under the curve).

The Product Insert for Serocion® (Appendix A) reports that for a 15 mg dose of propagermanium administered in a capsule to healthy adults, the plasma concentration of the drug peaked at about 3 hours and the biological half-life was about 2.5 hours. The reported tmax was 2.8 ± 0.2 hours, the Cmax was 0.174 ± 0.029 µg/mL, the t1/2 was 2.4 ± 0.2 hours.

There are no known metabolites of repagermanium in animals or humans. The Serocion® product label notes that when a single-dose of propagermanium 120 mg was orally administered to healthy adults, it was confirmed that a structural unit (3-oxygermyl-propionic acid) was not metabolised. The Serocion® product insert also notes that when a single-dose of propagermanium 30 mg was orally administered to healthy adults, 41.9% of the drug was excreted into urine within 24 hours and 50.1% of the drug was excreted into faeces within 72 hours.

The Serocion® Drug Product Interview form (Appendix B) includes details on the food effect on propagermanium following a single 30 mg dose in N=5 volunteers. In the fed group, compared to the fasting group, the tmax increased from 3.2 ± 0.2 to 3.8 ± 0.2 hours. The Cmax was approximately half in the fed group (0.137 ± 0.009 μg/mL) compared to the fasting group (0.269 ± 0.031 μg/mL) to. The t1/2 was similar in the 2 groups; 2.4 ± 0.07 in the fasting group and 2.19 ± 0.06 hours in the fed group. The total exposure as the area under the curve was approximately half that in the fed group compared with the fasting group, decreasing from 1.77 ± 0.17 in the fasting group to 0.838 ± 0.060 μg/mL/hour in the fed group. Also, the urinary excretion rate was approximately double in the fasting group at 41.9 ± 3.7 compared with the fed group 20.7 ±1.9 %.

Taken together, it is likely that food decreases the maximum concentration of propagermanium in the blood without significantly altering the time kinetics due to binding propagermanium to food and excretion without absorption. These data support DMX-200 being administered on an empty stomach to maximise bioavailability.

5.3 Safety and Efficacy in Humans

5.3.1 Dimerix Study DMX-200-101

Dimerix has completed a study investigating the safety of an immediate release capsule and extended release tablet formulation of DMX-200 as a secondary objective in the pharmacokinetic study DMX-200-201.

Safety findings in the 15 participants who received 120 mg capsule and 120 mg tablet DMX-200 (with and without food) as a single-dose demonstrated DMX-200 was safe and well tolerated at this dose.

The key safety findings observed in this study included:

- Across all treatment groups, 12 (80.0%) participants had at least 1 TEAE with a total of 28 events reported.
- The frequency of TEAEs was roughly equivalent in the fasted condition for both the capsule and tablet formulations with 11 events in 6 (46.2%) participants in the capsule group and 12 events in 7 (50.0%) participants in the tablet group.
- Across all treatment groups, the most frequently reported TEAEs by system organ class (SOC) were gastrointestinal disorders with 8 events in 6 (40.0%) participants. Events reported by more than 1 participant per treatment group included 2 participants reported diarrhoea (capsule fasted group) and 2 participants reported vomiting (tablet fasted group). There were no gastrointestinal events reported in the tablet fed group.

- Other TEAEs reported by more than 1 participant per treatment group included 2 participants reported catheter site pain (tablet fasted group), 2 participants reported vessel puncture site bruise (capsule fasted group) and 2 participants reported headaches (tablet fed group).
- The majority of TEAEs were mild (World health Organisation Grade 1). There were no severe TEAEs, regardless of assigned treatment.
- Treatment-related events included diarrhoea (2 events in the capsule fasted group), nausea and vomiting (both events in 1 participant in the tablet fasted group), palpitations (1 event in the capsule fasted group), arthralgia (1 event in the tablet fasted group) and headaches (1 event in the capsule fasted and tablet fed groups).
- One participant was withdrawn due to the TEAE of mild dizziness. The event was reported on Day 2, 30 hours after administration of tablet (fasted) in the first dosing period. It resolved 45 minutes after onset and was deemed not related to study drug administration.
- There were no SAEs reported during the study. There were no clinically significant events following treatment associated with abnormal laboratory findings, vital signs and ECGs.

5.3.2 Dimerix Study DMX-200-201

Objectives: The primary objective of the study was to determine the safety and tolerability of DMX-200 when added to irbesartan treatment in patients with proteinuric kidney disease. Secondary objectives included the investigation of biomarkers of kidney function.

Methods: The study was an open-label, non-randomised, dose escalation study conducted in patients with proteinuria. The study was planned in 2 parts; Part A (dose escalation) and Part B (dose expansion). As Part B was not initiated no results for Part B are reported here.

A total of 27 patients were enrolled into Part A and started a 14-day irbesartan-only run-in period, followed by a period of combined treatment (irbesartan and immediate release DMX-200). The starting dose for each patient was 10 mg DMX-200 TID (total daily dose [TDD] of 30 mg) for 28 days increasing in a step-wise manner as follows:

- Starting Dose: 10 mg TID (TDD = 30 mg) for 28 days.
- Escalation 1: 20 mg TID (TDD = 60 mg) for 28 days.
- Escalation 2: 30 mg TID (TDD = 90 mg) for 28 days.
- Escalation 3: 50 mg TID (TDD = 150 ng) for 28 days.
- Escalation 4: 80 mg TID (TDD = 240 mg) for 28 days.

The decision to escalate the dose was dependent upon a review of the safety data and proteinuria status. Patients with persistent proteinuria above the normal range at the end of a dosing period were increased to the next dose for a further 28 days. Patients with no proteinuria or proteinuria within normal limits at any visit were maintained on their current dose, which became that patient's final dose.

If a patient showed no proteinuria or proteinuria within normal limits for 2 successive 28-day dosing periods, DMX-200 dose escalation was complete. If a patient reached the end of

Escalation 4 and their proteinuria was not within normal limits, they were maintained on that dose for a further 56 days (total of 12 weeks at 240 mg TDD).

If a positive effect on proteinuria was observed at any dose but a patient indicated symptoms or safety concerns, then the dose could be reduced to a lower dose and this dose could then become the patient's final dose.

The population of patients selected for this study were males or females aged ≥ 18 years with previously diagnosed protein in the urine and a protein/creatinine ratio of ≥ 50 mg/mmol based on 24-hour urine collection. Patients were also required to meet a pre-defined level of kidney function, be taking a stable dose of irbesartan for at least 90 days prior to baseline and have a liver function test ≤ 2 x the upper limit of normal. The study excluded patients who had rapidly progressing proteinuria, acute kidney injury within 3 months of screening, were using particular medications, or had cancer, gastrointestinal bleeding, uncontrolled blood pressure or unstable heart disease.

Patients were screened from -14 days prior to dose administration. Patients attended the unit on Day 0 to undertake baseline assessments and clinic staff dispensed the necessary quantities of propagermanium required for 28-day dosing. Patients returned to the unit every 28 days until they reached their final dose. Once patients reached their final dose, they were maintained on that dose for a further 56 days, whereby DMX-200 dosing was complete. Patients returned to the unit for a follow-up visit 28 days after dosing was complete

Safety Results:

During the study, 27 patients received at least 1 dose of DMX-200 and 23 (85.2%) patients completed the study per protocol. There were 4 (14.8%) patients withdrawn due to TEAE's, 3 (11.1%) of which were SAEs.

The majority of patients that received at least 1 dose of DMX-200 (n=22 [81.5%]) reached a final dose of 240 mg, 3 of these were withdrawn due to AEs, with 19 completing the study per protocol. Two (7.4%) patients finished with a final dose of 150 mg, both completing the study per protocol. One (3.7%) patient finished with a final dose of 90 mg and completed the study per protocol. One (3.7%) patient finished with a final dose of 60 mg and completed the study per protocol. One (3.7%) patient finished with a final dose 30 mg, and was withdrawn due to an AE.

There were more males (n=22 [81.5%]) than females (n=5 [18.5%]) in the study, the median age across all patients was 61.0 years, and the majority of patients were Caucasian. A mean body weight of 88.7 kg and mean body mass index of 30.6 kg/m^2 was noted for all patients. Overall, the most common renal primary diagnoses were diabetic nephropathy (n=7), IgA nephropathy (n=5), and other proteinuric diseases (n=15).

The following key findings were observed in relation to TEAEs:

- Overall, 22 (81.5%) patients reported at least 1 TEAE with 121 events reported.
- Twenty-one events in 7 (25.9%) patients were deemed treatment-related. By dose level, treatment-related TEAEs occurred at the highest frequency in the 30 mg dose group

followed by the 90 mg dose group. The frequency was roughly equivalent across the remaining dose groups (60 mg, 150 mg and 240 mg). There were no clinically significant patterns of note associated with treatment-related TEAEs, regardless of propagermanium dose level.

- There were no trends between TEAE intensity and dose. Across all treatment groups, the majority of TEAEs were mild or moderate (similar incidence of mild and moderate TEAEs, regardless of DMX-200 dose level).
- There were no trends between TEAEs by SOC or preferred term (PT), regardless of DMX-200 dose level. The most frequently reported TEAEs by PT were hypertension (reported by 4 patients), and anaemia, viral upper respiratory tract infection, back pain, dizziness, increased daytime urinary frequency, asthma, and orthostatic hypotension (each reported by 2 patients). All other TEAEs occurred in no more than 1 patient and there were no trends of concern by SOC, regardless of dose level.
- Ten SAEs in 5 (18.5%) patients were reported. Of these, only one SAE (suicidal depression) was deemed possibly related to treatment. This event was reported 12 days into treatment with 240 mg DMX-200 (4 months and 2 days since first dose of IMP) and was subsequently withdrawn from the study.
- The annualised rate (events/days) for the total number of TEAEs was roughly equivalent across TEAE type and at each DMX-200 dose level. For severity of TEAEs, the annualised rate was similar for each classification (mild, moderate or severe) at each dose level, with the exception of DMX-200 dose 240 mg which reported an approximate 2-fold increase in moderate TEAEs compared to all other dose levels.

The following key findings were observed for vital signs, ECGs, clinical laboratory parameters, physical examination:

- Vital signs: No trends of concern were noted at any DMX-200 dose level for both systolic and diastolic blood pressure. Clinically significant changes in blood pressure values were reported by the investigator included high normal, Grade 1 (mild) hypertension, or isolated systolic hypertension, with no trends in reporting for either DMX-200 dose level or protocol specified time point. One (3.7%) patient experienced Grade 2 (moderate) hypertension at screening, but at no other time point, and there were no blood pressure values that were classified as Grade 3 (severe) hypertension.
- ECGs: No trends of concern were noted at any DMX-200 dose level and no abnormality was deemed to be clinically significant by the investigator.
- Urinalysis: No clinically significant result reported.
- Haematology or clinical chemistry: No clinically significant abnormalities in haematology or clinical chemistry parameters evident, regardless of treatment.
- Physical examination: The majority of the physical examination findings were normal or abnormal but not clinically significant.

Efficacy Results:

The following key efficacy findings were observed in all patients that received at least 1 dose of DMX-200 (N=27):

- Overall, 6 (22.2%) patients achieved the pre-specified criteria of responders (ie, achieving normalisation of proteinuria or a ≥50% reduction in proteinuria). This was a response rate of 27% in the n=23 patients that completed the study protocol.
- Post-hoc analysis of patients with different primary renal diagnoses showed reduced mean albumin and protein to creatinine ratios in patients with diabetic nephropathy, but not with IgA nephropathy or other renal diagnoses.
- On average, mean albumin creatinine ratios, glomerular filtration rates, mean protein excretion and mean monocyte chemoattractant protein-1 levels remained stable from baseline through dose escalation for each dose level up to 240 mg.

Conclusions: Overall, DMX-200 was safe and well tolerated when added to irbesartan treatment in patients with proteinuria. The annualised rate (events/days) for the total number of TEAEs was roughly equivalent across AE type and at each propagermanium dose level. The maximum severity of TEAEs reported in the majority of patients was moderate, and the incidence of TEAEs was roughly equivalent across the lower dosing groups but approximately 2-fold higher following administration of 150 mg DMX-200 (severe TEAEs only) and 240 mg DMX-200 (mild, moderate and severe). There were no clinically significant trends associated with treatment-related TEAEs, regardless of dose level. The majority of SAEs reported occurred following administration of the highest dose level (240 mg) with only 1 event deemed to be possibly related to treatment.

Dimerix have chosen to develop DMX-200 as a 240 mg/day dose due to the relative safety of this dose compared to lower doses, and the significant (27%) response rate (achieving normalisation of proteinuria or a ≥50% reduction in proteinuria) to treatment in patients that completed the study.

5.3.3 Dimerix Study DMX-200-202

Objectives: The primary objective of the study was to determine the safety and efficacy of DMX-200 in patients with FSGS who were receiving irbesartan.

Methods: The study was a double-blind, randomised, placebo controlled, crossover study to assess changes in protein/creatinine ratio (PCR) with treatment with DMX-200.

A total of 8 patients were enrolled into the study and randomised to two sequence groups as follows:

- Treatment Group 1: 120 mg DMX-200 BID in Treatment Period 1 (16 week duration) and placebo BID in Treatment Period 2 (16 week duration).
- Treatment Group 2: Placebo BID in Treatment Period 1 (16 week duration) and 120 mg DMX-200 BID in Treatment Period 2 (16 weeks duration).

The study consisted of a 14-day Screening period (including a Screening visit and Baseline assessment prior to randomisation), two 16-week treatment periods (Treatment Period 1 and Treatment Period 2) with a 6-week washout period between the treatment periods, followed by a 4-week follow-up period. The total study duration per patient was approximately 45 weeks.

Patients received stable irbesartan 300 mg/day for a minimum of 3 months prior to study entry and continued the same regimen throughout the study including during washout. For patients not on

stable irbesartan therapy at the time of Screening, investigators could decide to switch such patients from their current anti-hypertensive regimen to irbesartan 300 mg/day, with a titration period of not more than 4 weeks. These patients were then required to return the study site after 3 months of stable irbesartan 300 mg/day administration for reconsent and Screening.

Safety Results:

During the study, all 8 patients received doses of DMX-200. There were no patients withdrawn due to TEAEs.

The patient demographic characteristics were generally well balanced in the study, with no notable differences between sequence groups. The overall mean age of the patients was 45.9 years (age range, 19 to 64 years). The proportion of male patients (5 patients [62.5%]) was slightly higher than female patients (3 patients [37.5%]). Of the 3 female patients, 2 were of childbearing potential (66.7%). The majority of patients were White (6 patients [75.0%]) and the patient population was predominantly of Not Hispanic or Latino ethnicity (7 patients [87.5%]). The overall mean patient body weight at Screening was 81.8 kg and the mean body mass index (BMI) at Screening was 28.3 kg/m^2. Patients in the DMX-200→Placebo sequence group had a higher mean body weight (86.4 kg versus 77.2 kg) and mean BMI (29.6 kg/m^2 versus 27.0 kg/m^2) than patients in the Placebo→DMX-200 sequence group.

The addition of DMX-200 240 mg/day to stable irbesartan treatment in patients with primary FSGS was well tolerated when administered over 16 weeks of treatment:

- No TEAEs in the DMX-200 group were considered IMP-related by the investigator, and no concerns were identified relative to the known safety profile of DMX-200.
- The most frequently reported TEAEs (≥2 patients in any treatment group) during the study were hypertension and decreased appetite; the frequencies of these events were comparable between DMX-200 and placebo groups. None of the TEAEs assigned to DMX-200 or placebo were considered IMP-related. In the placebo group, 1 patient experienced a TEAE (dizziness) that was considered related to irbesartan. One patient in the placebo→DMX-200 sequence group experienced an unassigned TEAE (contusion) that was considered as possibly related.
- The majority of patients experienced TEAEs that were mild or moderate in severity. In the DMX-200 group, 1 patient had a severe non-serious TEAE (chest pain); this event was considered as unrelated to DMX-200 or irbesartan by the investigator.
- All patients (100%) experienced at least 1 TEAE during the study. The frequency of TEAEs was similar between the DMX-200 and placebo treatment periods. Four patients (50%) also experienced at least 1 TEAE during the study that was unassigned to a treatment.
- One SAE (tendonitis) was reported in the DMX-200 group during the study. This event was considered unrelated to DMX-200 or irbesartan by the investigator.
- No TEAEs resulted in study treatment or study discontinuation and no TEAEs resulted in death during the study period.

There were no clinically relevant findings or observations of note in clinical laboratory parameters, vital signs, or ECG results. The majority of physical examination findings not present at baseline were associated with TEAEs that were deemed NCS.

The following key findings were observed for vital signs:

- There were no clinically meaningful changes in vital signs parameters from baseline to the end of the follow-up period in either treatment group, and no notable differences between treatment groups.
- Two patients in the placebo→DMX-200 sequence group reported TEAEs of hypertension (exacerbation of hypertension) that corresponded with blood pressure derangements during the study (1 patient had 1 event assigned to DMX-200, and the other patient had 2 events assigned to both DMX-200 and placebo). All 3 events were mild and considered not related to IMP or irbesartan; all 3 events had resolved by the end of the study.

The following key findings were observed for clinical laboratory parameters:

- There were no notable changes in the mean values for haematology parameters from baseline to the end of the follow-up period in either group, except for platelet count (−36.3 $\times 10^9$/L in the DMX-200 group versus +34.0 $\times 10^9$/L in the placebo group). The change from baseline in platelet count was not clinically meaningful; the mean values were still within the normal range at the Follow-up visit.
- Compared with baseline, there were no notable increases in the number of patients with low or high values for haematology parameters. There were also no clinically significant haematology-related abnormalities that were reported as TEAEs. There were no clinically meaningful changes in the mean values for biochemistry parameters from baseline to the end of the Follow-up period in either group, and no notable differences between treatment groups.
- Compared with baseline, there were no notable increases in the number of patients with low or high values for biochemistry parameters; there were no effects on liver function enzymes (ALT or AST) following treatment
- Compared with baseline, there were no notable increases in the number of patients with low or high values for urine chemistry parameters.
- Compared with baseline, there were no notable increases in the number of patients with abnormal not clinically significant findings for urinalysis macroscopy parameters at the Follow-up visit based on the investigator's assessment. One patient had abnormalities in urine microscopy parameters (mucous, hyaline casts, granular casts, cellular casts, and bacteria) which were considered as clinically significant by the investigator; these abnormalities were not reported as TEAEs.

Efficacy Results:

The following key efficacy findings were observed in patients that received at least 1 dose of DMX-200 (N=8):

- The overall (Treatment Periods 1 and 2 combined) mean urine PCR at baseline was higher in the DMX-200 group (361.0 mg/mmol) compared with the placebo group (285.6 mg/mmol).
- Following 15/16 weeks of treatment with DMX-200 or placebo, the mean decrease (improvement) in urine PCR (Treatment Periods 1 and 2 combined) from Baseline was greater in the DMX-200 group (Δ = −84.3 mg/mmol) compared with the placebo group (Δ = −5.1 mg/mmol), with a difference of −79.2 mg/mmol between groups. The median change from baseline was also higher in the DMX-200 group (Δ = −55.4 mg/mmol) compared with the placebo group (Δ = +11.8 mg/mmol), with a median difference of −32.8 mg/mmol between groups.
- In the mixed model repeated measures analysis of treatment effect using a random effects mixed model and the log-transformed urine PCR values, the placebo-corrected ratio (DMX-200 versus placebo) was 0.88. The placebo-corrected ratio was less than 1, indicating a greater reduction in urine PCR in the DMX-200 group compared with the placebo group. The difference was not statistically significant (nominal p-value >0.05). No sequence effect or period effect was observed (nominal p-values >0.05).

Conclusions: Overall, DMX-200 was safe and well tolerated when added to irbesartan treatment in patients with FSGS. No TEAEs were considered treatment related to either DMX-200 or placebo. The positive signals from the efficacy/pharmacodynamic results, in particular with reduction in proteinuria, suggest that treatment with DMX-200 may result in clinically meaningful improvements in kidney function when added to the standard of care in patients with primary FSGS.

5.3.4 Dimerix Study DMX-200-203

Objectives: The primary objective of the study was to determine the safety and efficacy of DMX-200 in patients with DKD who are receiving irbesartan.

Methods: The study was a double-blind, randomised, placebo controlled, crossover study to assess changes in albumin/creatinine ratio (ACR) with treatment with DMX-200.

A total of 45 were enrolled into the study and randomised to two treatment groups as follows:

- Treatment Group 1: 120 mg DMX-200 BID in Treatment Period 1 (12 week duration) and placebo BID in Treatment Period 2 (12 week duration).
- Treatment Group 2: Placebo BID in Treatment Period 1 (12 week duration) and 120 mg DMX-200 BID in Treatment Period 2 (12 week duration).

The study consisted of a 14-day Screening period (including a Screening visit and Baseline assessment prior to randomisation), two 12-week treatment periods (Treatment Period 1 and Treatment Period 2) with a 6-week washout period between the treatment periods, followed by a 4-week follow-up period. The total study duration per patient was approximately 37 weeks.

Patients received stable irbesartan 300 mg/day for a minimum of 3 months prior to study entry and were to continue the same regimen throughout the study including during washout. For patients who were not on stable irbesartan therapy at the time of Screening, patients could switch from

their current anti-hypertensive regimen to irbesartan 300 mg/day, with a titration period of not more than 4 weeks. These patients were then required to return to the study site after 3 months of stable irbesartan 300 mg/day administration for re-consent and Screening.

Safety Results:

During the study, all 45 patients received DMX-200. Two patients (one in the DMX-200 group and one in the placebo group) were withdrawn due to TEAEs.

A total of 45 patients were enrolled into the study and randomised to one of the sequence groups, Placebo→DMX-200 (23 patients) or DMX-200→Placebo (22 patients). The patient demographic characteristics were generally well balanced in the study, with no notable differences between sequence groups. The overall mean age of the patients was 66.8 years, and there were more male patients enrolled in the study (42 men versus 3 women). The majority of patients were White (75.6%) and the patient population was predominantly of Not Hispanic or Latino ethnicity (97.8%).

Overall, the addition of DMX-200 240 mg/day to stable irbesartan treatment in patients with DKD was well tolerated when administered over 12 weeks of treatment. The reported TEAEs were consistent with natural history of DKD and events seen in a general patient population. No concerns were identified relative to the known safety profile of DMX-200.

- Overall, 6 patients in each group reported at least 1 IMP-related TEAE. No severe IMP-related TEAEs were reported.
- The nature, severity, and frequency of TEAEs following DMX-200 administration were similar to those observed following placebo administration. The most frequently reported TEAEs during the study were oedema peripheral, nasopharyngitis, upper respiratory infection and hypertension; the frequencies of these events were comparable between DMX-200 and placebo groups except for nasopharyngitis which had a higher frequency in the placebo group (13.3%) compared with the DMX-200 group (2.2%).
- The majority of patients experienced TEAEs that were mild or moderate in severity. The maximum severity of TEAEs (assigned and unassigned) for the majority of patients was mild or moderate. More patients in the DMX-200 group had severe TEAEs (6 patients [13.3%]) compared with the placebo group (2 patients [4.4%]). All severe TEAEs were considered not related to the IMP or irbesartan by the investigator.
- The frequency of patients who experienced TEAEs was similar between the placebo and PPG groups (64.4% and 60.0%, respectively). Twelve patients (26.7%) also experienced at least 1 TEAE during the study that was unassigned to a treatment. There were no notable differences in numbers of patients with TEAEs between sequence groups.
- The frequency of patients who reported at least 1 IP-related TEAE was low and identical in both groups (13.3%). No patients experienced an unassigned TEAE that was considered IP-related. One patient in the placebo group experienced a TEAE that was considered unlikely related to the IP but possibly related to irbesartan.
- Ten patients experienced a total of 13 SAEs during the study: 4 patients in the placebo group, 4 patients in the DMX-200 group, and 3 patients who reported SAEs that were unassigned to a particular treatment. The frequency of SAEs reported during the study following DMX-200

administration were similar to those observed following placebo administration, and all SAEs were considered to be not related to IMP by the investigator. Of the 13 SAEs, 7 were considered severe. In the DMX-200 group, a total of 4 severe SAEs were reported (appendicitis perforated, fall, device related infection and wound infection). In the placebo group, 1 patient reported 2 severe SAEs of anaphylactic reaction. The same patient (placebo→DMX-200 sequence group) experienced another severe SAE of anaphylactic reaction, which was unassigned to a particular treatment. Following the first episode of anaphylaxis, this patient was withdrawn from IMP (placebo) permanently but continued irbesartan treatment and remained in the study for follow-up assessments.

- Two patients (1 in the DMX-200 group and 1 in the placebo group) withdrew from IMP following TEAEs of moderate erythema multiforme and severe anaphylactic reaction, respectively. The TEAE of erythema multiforme was considered IMP-related. The anaphylactic reaction was considered a suspected unexpected serious adverse reaction not related to IMP.
- No TEAEs leading to death occurred during the study.

There were no clinically significant findings in the laboratory data including no changes in liver function enzymes (ALT or AST) following treatment. There were also no clinically significant changes in vital signs, ECGs, or physical examination during the study.

The following key findings were observed for vital signs:

- There were no clinically meaningful changes in vital signs parameters from baseline to the end of the Follow-up period in either group, and no notable differences between treatment groups.
- Three patients in the placebo group and 1 patient in the DMX-200 group reported TEAEs of hypertension. One patient reported hypertension that was unassigned to a particular treatment. Two patients in the placebo group and 1 patient in the DMX-200 group reported TEAEs of hypotension. Of these events, none were severe.

The following key findings were observed for clinical laboratory parameters:

- There were no notable changes in the mean values for haematology parameters from baseline to the end of the Follow-up period in either group, except for an increase in the mean corpuscular haemoglobin concentration (+6.0 g/L in the placebo group versus +9.6 g/L in the DMX-200 group) and a decrease in mean platelet count (-19.0×10^9/L in the placebo group versus -8.5×10^9/L in the DMX-200 group). These changes were not considered clinically meaningful; the mean values were still within the normal range at the Follow-up visit.
- Compared with baseline, there were no notable increases in the number of patients with low or high values for haematology parameters at the Follow-up period. In the DMX-200 group, 2 patients had TEAEs related to haematology parameters: 1 event of mild anaemia and 1 event of mild iron deficiency; both events were considered not related to IMP. The TEAE of anaemia had not resolved by the end of the reporting period. There were no notable changes in the mean values for biochemistry parameters from baseline to the end of the Follow-up period, except for creatinine concentration (+0.7 µmol/L in the placebo group compared with

+12.0 µmol/L in the PPG group). These changes were not considered clinically meaningful; the mean values were still within the normal range at the Follow-up visit.
- Compared with baseline, there were no notable increases in the number of patients with low or high values for biochemistry parameters at the Follow-up period.

The following clinically significant biochemistry-related abnormalities were reported as TEAEs:
- Hyperkalaemia: 2 patients in the placebo group; for 1 patient this was reported as a mild SAE and was unlikely related to IMP; for 1 patient this event was moderate in severity and considered as not related to IMP by the investigator. Both events had resolved at the end of the reporting period.
- Hypokalaemia: 1 patient in the placebo group experienced this mild TEAE that was considered to be not related to IMP. This event had resolved at the end of the reporting period.
- Gamma-glutamyltransferase increased: 1 patient in the placebo group experienced this event which was considered moderate in severity and not related to IMP. The event had resolved at the end of the reporting period.
- Hypercalcaemia: 1 patient in the DMX-200 group experienced this mild TEAE that was considered to be possibly IMP-related. The event had not resolved at the end of the reporting period.
- Hypoglycaemia: 1 patient in the DMX-200 group experienced this mild TEAE that was considered to be unlikely related to IMP. This event had resolved at the end of the reporting period.

Efficacy Results:

- Following 11/12 weeks of treatment, the mean decrease (improvement) in urine albumin/creatinine ratio (ACR) (Treatment Periods 1 and 2 combined) from Baseline was slightly greater in the DMX-200 group (Δ = −9.17 mg/mmol) compared with the placebo group (Δ = −6.92 mg/mmol), with a mean difference of −2.24 mg/mmol. Although not statistically significant, the placebo-corrected ratio in the MMRM analysis of treatment effect was less than 1, indicating a greater reduction in urine ACR in the DMX-200 group compared with the placebo group.
- Reduction in urine ACR of ≥20%, ≥30%, or ≥40% during the study or after 11/12 weeks of treatment was similar for the DMX-200 group and the placebo group.
- Following 11/12 weeks of treatment, the mean decrease (improvement) in 24-hour urine PCR from Baseline was greater in the DMX-200 group (Δ = −11.37 mg/mmol) compared with the placebo group (Δ = +0.03 mg/mmol). Although not statistically significant, the placebo corrected ratio in the MMRM analysis of treatment effect in urine PCR was less than 1.
- At 11/12 weeks of treatment, no notable changes were observed in total serum albumin concentrations in either group, whereas a greater decrease in total albumin excretion in urine from baseline was observed in the placebo group compared with the DMX-200 group. The treatment differences were not statistically significant. There were no notable changes in the other measures of proteinuria and kidney function from baseline in either group, and no substantial treatment group differences were observed.

- Following 11/12 weeks of treatment, no notable changes were observed in serum biomarker HbA1c and C-peptide concentrations in either group.
- In patients who received SGLT2 inhibitors, the results of the exploratory analysis of treatment differences in urine ACR and PCR values (placebo-corrected ratios were >1.0 for both parameters) and total albumin blood concentration (DMX-200 minus placebo, +0.55 g/L) at 11/12 weeks of treatment versus Baseline, indicating little or no reduction in these parameters in the DMX-200 group compared with the placebo group.

Conclusions: Oral administration of DMX-200 240 mg/day for 12 weeks was safe and well tolerated in patients with DKD, with a safety profile similar to that observed with placebo.

5.3.5 Safety and Efficacy of Propagermanium (Serocion®) in Patients with Chronic Hepatitis B

Extensive evidence for the safety of propagermanium has been provided to the Japanese PDMA for the licensure of Serocion® for the treatment of chronic hepatitis B.

Clinical studies used to support licensure of Serocion® included:

- A study of 5 healthy, fasting adult men were given single-doses of immediate release propagermanium capsules of 15, 30, 60, 120 and 240 mg, and another 30 mg single dose after meals (Madoka I, 1990). No abnormalities were observed following examination for subjective symptoms, auscultation, physiological symptoms, and clinical laboratory tests (ECG, blood biochemistry, haematology, endocrine, urinalysis).
- A study of postprandial administration of 60 mg of propagermanium in 5 healthy adult men 3 times daily over a 7-day period (Ito K, 1990). No abnormalities believed to be caused by propagermanium were observed following examination for subjective symptoms, auscultation, physiological symptoms, and clinical laboratory tests.
- A study of 121 patients presenting with chronic hepatitis B (Hirayama C, 1990a). Patients were divided into 3 groups receiving 30, 60, or 90 mg/day of propagermanium over a 12-week period, and clinical utility, optimal dosage, and safety were evaluated. By Week 12, patients in the 30 mg/day group exhibited significant improvement in liver biomarkers including AST, alkaline phosphatase (ALP) and gamma-glutamyl transferase levels. The severity of liver function tests including significantly decreased hepatitis B antigen (HBeAg) levels were also observed. Better than marginal utility was observed more frequently in the 30 mg/day group and was determined to be the optimal dose. No severe adverse drug reactions were observed.
- A study of 78 patients with chronic hepatitis B (Hirayama C, 1990b). Patients were given 15 or 30 mg/day propagermanium over a 12-week period as part of a double-blind study to evaluate clinical utility, optimal dosage, and safety. Patients in the 30 mg/day group exhibited improved liver function and clinical utility in comparison with the 15 mg/day group. Patients in the 30 mg/day group exhibited significant decreases in AST and ALP, and superior rates of decline in HBeAg levels. Accordingly, 30 mg/day was determined to be the optimal dose. No severe adverse drug reactions were observed.

- A study of 182 patients with chronic hepatitis B (Hirayama, 1990c). 101 patients were given 30 mg/day of propagermanium and 81 patients were given a placebo over a 16-week period as part of a double-blind study. Patients in the propagermanium group exhibited significantly superior improvement in liver function as well as overall improvement compared with the placebo group. After 16-weeks dosing, patients in the propagermanium group exhibited significant improvements in AST, ALP, total cholesterol, and gamma-globulin levels in comparison with the placebo group. In addition, propagermanium group patients exhibited higher HBeAg and hepatitis B antibody levels in comparison with the placebo group. Observed adverse reactions were minor.
- A study of 34 patients with chronic hepatitis B (Yano T, 1990). 10 mg of propagermanium was given TID over a 1-year period. Efficacy and safety were assessed using liver histological images and liver function tests. Significant decreases in AST and ALP levels were observed 16 weeks after administration. Adverse reactions occurred in 1 patient (skin eruption, itching, general languor) but were not considered serious.

In summary, propagermanium administered as an immediate release formulation (Serocion®) up to 240 mg/day was shown to be safe in healthy volunteers, and a safe and effective in patients with chronic hepatitis B at doses of 30 mg/day.

Safety signals observed in patients with chronic hepatitis were generally related to the acute exacerbation of chronic hepatitis B hepatic effects (see safety warnings in Appendix A) including:

- Raised AST.
- Raised ALP.
- Malaise.

Additionally, depression with suicidal ideation was reported in 1 patient with myeloma in a single study (Tsutsumi, et al. 2004).

5.4 Marketing Experience

DMX-200 is not yet approved for marketing in any territory globally. Dimerix has not yet submitted any marketing applications for the product, and no applications have been rejected or withdrawn in any regulatory jurisdiction.

Propagermanium has been available as a prescription product (Serocion®) in Japan since 1994 and is approved for the treatment of chronic hepatitis B infection (Anon., The Pharma Letter 1994). Repagermanium has also been available as a nutritional or dietary supplement since the 1970s in Japan and in other countries including the UK since the 1980s (Kaplan, et al., 2004). Repagermanium is available for purchase as a dietary supplement via on-line suppliers in Australia and the USA, with recommended doses commonly greater than 1000 mg per day.

Dimerix is not aware of the rejection or withdrawal of marketing applications for Serocion® in any regulatory jurisdiction.

6. SUMMARY OF DATA AND GUIDANCE FOR INVESTIGATOR

6.1 Indications and Usage

DMX-200 is an IMP for the treatment of moderate or severe ARDS in patients with suspected or confirmed COVID-19.

In the planned studies repagermanium will be administered as a dose of 120 mg twice daily (TDD 240 mg).

6.2 Supply, Storage and Stability

DMX-200 will be supplied in primary packaging of white high density polyethylene bottles containing 30 capsules.

DMX-200 capsules have a shelf life of 12 months when stored at 15 - 25°C (with excursions permitted up to 30°C).

6.3 Non-clinical Summary

Repagermanium shows relatively low acute and repeat-dose toxicity.

The oral LD50 of propagermanium are 7050 mg/kg in rats, 5600 mg/kg in mice, and greater than 4000 mg/kg in dogs. (Kanda K. 1990) (S. M. Miyazaki Y 1990)

Repeat oral-dose nonclinical toxicology studies show the lowest no observable adverse effect level (NOAEL) in a 3-month study in rats was at a human equivalent dose (HED; assuming body weight of 60 kg) of 2.46 g/day, with a reduction in weight gain, water intake and stool consistency at higher doses. (Sanwa 2010) A 3-month subacute toxicology in dogs suggested that the NOAEL was lower than the lowest dose tested equivalent to a HED of 9.75 g/day, with excretion of loose stools, muddy stools and watery stools observed at the lowest dose. (S. M. Miyazaki Y 1990) A 12-month oral-dose study in rats identified a NOAEL at a HED of 0.846 g/day, with increased kidney weight at higher doses. (Nakagawa H 1990) However, a 12-month oral-dose study in dogs identified a higher NOAEL at the HED of 2.88 g/day, with diarrhoea, vomiting, and weight loss at higher dosages. (S. M. Miyazaki Y 1990)

The information available on the kinetics and metabolism of repagermanium suggests low potential for drug-drug interactions.

6.4 Clinical Summary

A dose of 30-240 mg/day of an immediate release formulation of propagermanium in the registered Japanese product Serocion® has been shown to be safe in healthy volunteers, and a dose of 30 mg/day has been shown to be safe and effective in patients with chronic hepatitis B (**Section 5.3.5**). Adverse events are predominantly related to exacerbation of acute symptoms of hepatitis B in these patients (see Appendix A).

Dimerix has completed a Phase 1 pharmacokinetic, metabolism and safety clinical study (DMX-200-101, Section **5.2.1** and Section **5.3.1**) investigating 120 mg immediate release capsule and 120 mg extended release tablet of DMX-200 (with and without food) administered as a single-dose in healthy volunteers and 3 clinical studies with DMX-200 administered to patients with proteinuric kidney disease, DKD and FSGS already receiving an angiotensin receptor blocker:

- Study DMX-200-201 (**Section 5.3.2**). A total of 27 patients were enrolled and started a 14-day irbesartan-only run-in period, followed by a period of combined treatment (irbesartan and immediate release DMX-200). The starting dose for each patient was 10 mg DMX-200 TID ([TDD] of 30 mg) for 28 days increasing in a step wise manner to 20 mg TID (TDD = 60 mg) for 28 days, 30 mg TID (TDD = 90 mg) for 28 days, 50 mg TID (TDD = 150 mg) for 28 days, and finally 80 mg TID (TDD = 240 mg) for 28 days.
- Study DMX-200-202 (**Section 5.3.3**). A total of 8 patients were enrolled into the study to determine the safety and efficacy of DMX-200 in patients with FSGS. The study was a double-blind, randomised, placebo controlled, crossover study to assess changes in PCR with treatment with DMX-200. Patients received either 120 mg DMX-200 BID in Treatment Period 1 (16 week duration) and placebo BID in Treatment Period 2 (16 week duration) or placebo BID (16 week duration) and DMX-200 BID in Treatment Period 2 (16 week duration).
- Study DMX-200-203 **(Section 5.3.4**). A total of 45 patients were enrolled into the study to determine the safety and efficacy of DMX-200 in patients with DKD who were receiving irbesartan. The study was a double-blind, randomised, placebo controlled, crossover study to assess changes in ACR following treatment with DMX-200. Patients received 120 mg DMX-200 BID in Treatment Period 1 (12 week duration) and placebo BID in Treatment Period 2 (12 week duration) or placebo BID in Treatment Period 1 (12 week duration) and 120 mg DMX-200 BID in Treatment Period 2 (12 week duration).

6.4.1 Pharmacokinetics

The pharmacokinetics of 120 mg immediate release DMX-200 in a capsule was investigated in a Phase 1 study completed by Dimerix (refer to **Section 5.2.1**).

The study demonstrated:

- Mean plasma repagermanium concentration over time profiles showed an initial peak over 3 to 5 hours followed by a mono exponential decline.
- Mean repagermanium urine concentration over time profiles showed an initial peak during the 4 to 8 hours post-dose time point followed by a mono exponential decline.
- Following a single-dose of 120 mg DMX-200:
  - Mean Cmax was 813.8 ng/mL.
  - Mean AUC(0-last) was 5298 h/ng/mL.
  - Mean tmax was 3.25 hours.
  - Mean t½ was 3.57 hours.

Pharmacometric modelling shows linearity between repagermanium exposure in plasma between the doses used in the Phase 1 and Phase 2 studies.

6.4.2 Safety

Whilst DMX-200 has not yet been tested in the respiratory setting, it has an extensive safety database with a low AE profile unlike many immune modulators.

Dimerix has completed 4 clinical studies of DMX-200:

- A healthy volunteer study (N=15), investigating 120 mg immediate release capsule and 120 mg extended release tablet.
- A study of DMX-200 in patients with proteinuric kidney disease (N=27), dose escalation study of DMX-200 with irbesartan.
- A study of DMX-200 in patients with FSGS (N=8), investigating 120 mg DMX-200 BID concurrently with irbesartan.
- A study of DMX-200 in patients with DKD (N=45), investigating 120 mg DMX-200 BID concurrently with irbesartan.

The safety database for DMX-200 therefore contains data from N=95 individuals. This includes data for 15 healthy volunteers and 80 patients with renal impairment. These studies administered DMX-200 at daily doses from 30 to 240 mg for a duration of up to 28 weeks. Adverse drug reactions (ADRs) reported in Dimerix sponsored clinical studies are summarized in **Table 13**.

Table 13 Adverse Drug Reactions Associated with DMX-200

System Organ Class Preferred Term	**Number of participants to report the ADR**	**Total number of ADRs reported**	**Severity of ADRs reported**
Cardiac Disorders			
Palpitations	1	1	Mild
Ear and labyrinth disorders			
Tinnitus	1	1	Mild
Gastrointestinal disorders			
Diarrhoea	2	2	Mild
Nausea	2	2	Mild
Vomiting	1	1	Mild
Abdominal distention	1	1	Mild
General disorders and administration site conditions			
Chest pain	1	1	Moderate
Oedema peripheral	2	2	Mild
Feeling hot	1	1	Mild
Investigations			
Blood bicarbonate decreased	1	2	Moderate
Blood creatinine increased	2	2	Mild
Blood magnesium decreased	1	1	Mild
Glomerular filtration rate decreased	1	1	Mild
Haemoglobin decreased	1	1	Moderate
Urine output increased	1	1	Moderate
Metabolism and nutrition disorders			
Hyperkalaemia/ Blood Potassium Increased	2	3	Mild/Moderate
Hypercalcaemia	1	1	Mild

System Organ Class Preferred Term	**Number of participants to report the ADR**	**Total number of ADRs reported**	**Severity of ADRs reported**
Musculoskeletal and connective tissue disorders			
Arthralgia	1	1	Mild
Nervous system disorders			
Headache	1	2	Mild
Dizziness	1	1	Mild
Dysgeusia	1	1	Mild
Memory impairment	1	1	Mild
Psychiatric disorders			
Depression suicidal	1	1	Moderate
Sleep disorder	1	1	Moderate
Renal and urinary disorders			
Pollakiuria	2	2	Mild
Dysuria	1	1	Mild
Renal impairment	1	1	Moderate
Skin and subcutaneous tissue disorders			
Hyperhidrosis	1	1	Mild
Erythema multiforme	1	1	Moderate

Abbreviations: ADR = adverse drug reaction

The most frequently reported ADRs included hyperkalaemia/blood potassium increased (3 ADRs reported by 2 participants [2.1%]).

Other ADRs reported by at least 2 participants (2.1%) include blood creatinine increased, diarrhoea, nausea, oedema peripheral, and pollakiuria.. All remaining ADRs were reported by 1 participant only (1.1%). ADRs that were reported twice by 1 participant include Blood bicarbonate decreased and Headache.

One serious ADR has been reported through Dimerix sponsored clinical studies:

- Depression suicidal was reported by participant 02A03 in study DMX-200-201, a 40 year old white male patient with CKD who was 12 days into treatment with 240 mg DMX-200 (and 4 months and 2 days since first dose of study drug). The event met the criteria for seriousness as a medically important event. This event was considered moderate in intensity and possibly related to DMX-200. IMP was discontinued permanently. The patient reported experiencing intermittent depression with suicidal ideation. At a follow-up visit 22 days post reporting the event, the patient reported cessation of depression and suicidal ideation, and reported clearer thinking. Unfortunately the medical history collected at study entry did not capture psychiatric history in study participants, however a high prevalence of depression and anxiety is seen among patients with CKD. Indeed, it is estimated that 23.7% of patients with CKD have depression (Mosleh, et al., 2020).

Propagermanium as Serocion® has been formally evaluated for safety in a total of 2,015 patients. Reported AEs for Serocion® (indicated for chronic hepatitis B) include elevated AST, elevated ALT, malaise and loss of appetite. The full list of AEs is included in Appendix A. Depression was also reported as a possible adverse effect in a single study in multiple myeloma patients (Hirayama, Suzuki, et al. 2003).

In repeat-dose toxicity studies of repagermanium, mild gastrointestinal events including diarrhoea were observed at 16-fold higher dose than proposed for clinical investigation and vomiting and slight weight loss were observed as acute effects in animals administered repagermanium at a 500-fold higher dose than proposed for clinical investigation.

6.4.3 Reference Safety Information for Assessment of Expectedness of Serious Adverse Events

No SARs are considered expected by the Sponsor for the purpose of expedited reporting of SUSARs and identification of SUSARs in the "Cumulative summary tabulation of serious adverse reactions" in the DSUR for the IMP.

6.4.4 Efficacy

Simultaneous intervention in AT1R and CCR2 signalling may benefit patients with ARDS as a result of viral infection caused by the SARS-Cov2 pathogen (COVID-19). However, there is no clinical efficacy data available to support this indication.

Study DMX-200-201: A significant (27%) response rate (defined as achieving normalisation of proteinuria or a ≥50% reduction in proteinuria) was observed in patients with proteinuria that completed the study. The response was only observed in patients receiving 300 mg irbesartan. *Note: this study was not powered for efficacy.*

Study DMX-200-202: Following 15/16 weeks of treatment with DMX-200, the mean decrease (improvement) in urine PCR from Baseline was $\Delta = -84.3$ mg/mmol for patients with FSGS, suggesting that treatment with DMX-200 may result in clinically meaningful improvements in kidney function when added to the standard of care in patients with primary FSGS. *Note: this study was not powered for efficacy.*

Study DMX-200-203: There were no statistically significant or clinically meaningful differences between DMX-200 and placebo in changes in ACR and PCR in patients with DKD. However, data suggest a possible treatment effect of DMX-200 in patients with higher baseline ACR values. *Note: this study was powered for efficacy.*

6.5 Contraindications

Propagermanium (as Serocion®) is contraindicated in patients with existing chronic hepatitis B with jaundice or hepatic cirrhosis due to the potential for increased severity of the disease, and in patients that are known to be hypersensitive to repagermanium or a component of the formulation containing lactose or magnesium stearate.

6.6 Warnings/Precautions

The product insert for Serocion® notes precautions the use of repagermanium in the target population of patients with hepatitis B. These include acute exacerbation of chronic hepatitis B.

However, specific guidance and precautions for management of patients with hepatitis are noted in the product insert if required.

6.7 Drug Interactions

Repagermanium is not known to interact with other drugs.

The safety and effectiveness of repagermanium in specific populations has not been established. There is no evidence for the safety or efficacy of repagermanium in specific populations including paediatric populations, during pregnancy and lactation, and the elderly.

6.8 Treatment of Overdose

Propagermanium as Serocion® is administered orally at 30 mg/day. Dimerix has investigated the range of doses between 30 and 240 mg/day. The use of repagermanium as a dietary supplement is often provided at doses > 1000 mg/day and human studies have used doses up to 4.0 g/day with no observed deleterious effects.

No specific information is available on the treatment of overdose with repagermanium. Should overdose occur, the patient should be monitored closely, and appropriate supportive care provided under the guidance of a clinician.

6.9 Patient Counselling

The use of DMX-200 as an IMP and should not be used outside of a regulated clinical research study.

Patients should be instructed to promptly report any adverse reactions to the investigator.

There is no evidence for the safety of repagermanium during pregnancy or breast feeding. Patients should avoid pregnancy during the study and agree to follow the contraceptive requirements outlined in the study protocol.

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8. DOCUMENT HISTORY

A summary of the changes which taken place between different versions of the Investigators Brochure are summarised below.

Table 14 Summary of Changes to Investigators Brochure

Version No.	Document Reference	Details of Changes
1.0	-	Original Version
2.0	Throughout	Streamlining of presentation of safety information including tabulation of ADRs
3.0	Pages 20, 30 & 32	Addition of Chronic Toxicity Study in Rodents (Reddeman 2020) to data tables and discussion
4.0	Throughout	Correction of typographical errors
	Page 8	Revision to frequency of ADRs, specifically removal of oedema peripheral from discussion on frequently observed ADRs
	Page 12	Removal of plot showing "effects of DMX-200 on urine protein creatinine ratio (uPCR) and uMCP".
	Pages 62 – 63	Revision of ADRs based on review, specifically correction of incidences of oedema peripheral from 3 to 2, and removal of melaena. Typographical correcton of event for blood magnesium – changed from increased to decreased. Removal of oedema peripheral from discussion on frequently observed ADRs
	Page 64	Section added for "Reference Safety Information for Assessment of Expectedness of Serious Adverse Events" (Section 6.4.3)

9. APPENDICES

APPENDIX A – SEROCION® PRODUCT LABEL

[barcode]

October 2009 revised (Ver. 5, revised with the abolition of the designated drug system)

February 2008 revised

Storage method Store at room temperature

Expiration date 3 years after manufacture (to be used before the expiration date indicated on the packaging)

Drug used for oral treatment of chronic hepatitis B

Standard Commodity Classification No. of Japan	873919

Approval no.	20600AMZ01109000
Date of listing on the NHI reimbursement price list	August 1994
Date of initial marketing in Japan	August 1994
Date of latest reexamination	November 2003

SEROCION® CAPSULE 10

SEROCION®

(Propagermanium capsule)

Note) Caution---Use only pursuant to the prescription of a physician, etc.

■ Warning ■

Chronic hepatitis sometimes is acutely exacerbated and deaths have been reported.

■ Contraindications (do not administer to the following patients) ■

(1) Patients with jaundice (chronic hepatitis B can become more severe)
(2) Patients with hepatic cirrhosis, or patients suspected of having hepatic cirrhosis (chronic hepatitis B can become more severe)
(3) Patients with a past history of hypersensitivity to the drug

■ Description ■

1. Composition

Serocion Capsule 10 is a formulation that contains the following ingredients and contents in a capsule:

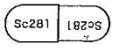
Propagermanium ….. 10mg

※ Hydroxypropyl cellulose, magnesium stearate, lactose hydrate and sodium lauryl sulfate in the capsule body are contained as additives.

2. Properties

Serocion Capsule 10 is a No. 4 hard capsule that is white at its head and white in its body.

The capsule is filled with a white granular powder that is odorless and has a slightly acidic taste.

	Head	Body
External form		
	White	White
ID code	Weight (content) mg	
Sc281	220(180)	

■ Indications ■

Improvement of viral markers in HBe antigen-positive chronic hepatitis B

■ Dosage and Administration ■

Normal adult subjects were orally administered propagermanium 30mg daily in a divided dose after each of 3 meals.

Precautions Regarding Dosage and Administration

Laboratory tests, including measurements of viral markers (HBe antigens, etc.), were performed in week 16 after the start of treatment. If no improvement of viral markers was observed, other treatment was to be considered.

■ Precautions for Use ■

1. Administer with caution (should be administered with caution to the following patients)

(1) A patient with a past history of drug hypersensitivity
(2) A patient with severe renal disorder [this drug is eliminated primarily by the kidneys, and its blood concentration reportedly rises in renal failure (unilateral nephrectomized) model rats.]
(3) A patient with a past history of jaundice [an acute exacerbation, etc., of chronic hepatitis B may appear.]
(4) A patient immediately after the administration of interferon has ended [immediately after the administration of interferon, the quantity of virus may increase and deterioration of liver function may occur.]
(5) An elderly patient [See “Administration to the Elderly”]

2. Important Basic Precautions

(1) When using this drug, it should be confirmed that the patient’s disease is **HBe-antigen positive**. Moreover, the transaminase level, albumin level, the coagulation system, platelet count, etc., should be determined and it should be confirmed that the disease is **chronic hepatitis without findings suspected to be liver lesions**.

(2) Since **acute exacerbation of chronic hepatitis B** may occur, attention should be paid to the following points.

1) When starting to administer this drug

When administering this drug, HBV-DNA (or DNA-P) should be measured and it should be confirmed that no conspicuous increase is observed (in chronic hepatitis B, an acute exacerbation accompanied by an increase in the amount of virus may occur during the disease’s natural course).

[barcode]

2) During administration of this drug
   a) When a sharp increase has been noted in a periodic measurement of HBV-DNA (or DNA-P), the administration of this drug should be discontinued and consideration should be given to the use of other therapy that might be appropriate (when a sharp increase in HBV-DNA (or DNA-P) has been observed, an acute exacerbation of chronic hepatitis B may appear).
   b) **Liver function tests should be performed periodically (especially immediately after treatment in in weeks 2, 4 and 6).**
   c) When **exacerbation of hepatic function disorder and jaundice** have appeared, the administration of this drug should be discontinued and appropriate treatment measures should be taken.
   d) When yellow staining of the eyeballs and skin and brown urine have been noticed, the patient should be immediately contacted and cautioned about them.

(3) To verify the clinical efficacy of this drug, attention should be paid to the following.
   1) During administration of this drug, laboratory tests should be performed every 4 weeks (liver function tests should be performed immediately after starting administration in weeks 2, 4 and 6 [see (2) above]).
   2) If HBe antigen is observed to have become negative, the administration of the drug should be ended.

3. Adverse Reactions

Of a total of 2,015 patients, adverse reactions were reported to occur in 221 patients (10.97%). The main symptoms were 38 episodes (1.89%) of elevated AST (GOT), 40 episodes (1.99%) of elevated ALT (GPT), 27 episodes (1.34%) of malaise and 18 episodes (0.89%) of loss of appetite [At end of reexamination]

(1) Clinically significant adverse reactions

Acute exacerbation of chronic hepatitis B: Since serious hepatic function disorder and hepatic failure accompanied by jaundice and a markedly elevated transaminase level may occur, observations, including periodic (in particular, immediately after treatment in weeks 2, 4 and 6) liver function tests, should be performed, and if abnormalities have been observed, administration should be discontinued and appropriate treatment measures should be taken.

(2) Other adverse reactions

	0.1 – <5%	<0.1%
Hypersensitivity[Note 1)]	Rash, pruritus, urticaria	Eczema
Digestive organs	Loss of appetite, abdominal pain, queasiness, vomiting, diarrhea, constipation, bloating, heartburn, stomatitis	Heavy stomach feeling
Neuropsychiatric system	Depression[Note1)], sleepiness, dizziness, headache, numbness of the hands and feet	Insomnia, tremor
Liver[Note 2)]	Jaundice, elevated AST (GOT), elevated ALT (GPT), elevated bilirubin	
Blood[Note 1)]	Eosinophilia	White blood cell decreased
Other	Menstrual abnormality, alopecia, malaise, elevated blood pressure	Fever, arthralgia, chest pain, edema

Note 1) If symptoms appeared, administration of the drug should be discontinued and appropriate treatment measures should be taken.
Note 2) If sufficient observations have been made and abnormalities have been discovered, appropriate treatment measures should be taken.

4. Administration to the Elderly

Administration to elderly patients should proceed with caution, starting from a low dose (for example, 20mg a day), etc., and observing the patient's condition. [This drug is excreted primarily by the kidneys, but since renal function declines in the elderly, there is a possibility that the drug's blood concentration will rise.]

5. Use during Pregnancy, Delivery or Lactation

(1) Should be administered to women who are pregnant or potentially pregnant only if the benefits of treatment are judged to outweigh the risks. [The safety of administration of the drug has not been established in pregnant women.]

(2) Administration to women who are lactating should be avoided, and if the drug has to be administered, lactation should be discontinued. [It has been reported that the drug transfers to breast milk in animal studies (rat).]

6. Pediatric Use

The safety of administering the drug to children, etc., has not been established (there is insufficient clinical experience).

7. Precautions Concerning Use

Caution when handing over drug: Patients should be instructed to orally take drugs that are in PTP packaging after pressing the drug through the PTP sheet. (If the PTP sheet is swallowed accidentally, a hard, sharp-cornered object may become implanted in the esophageal mucous membrane, and serious complications such as the occurrence of a perforation and mediastinal sinusitis are being reported)

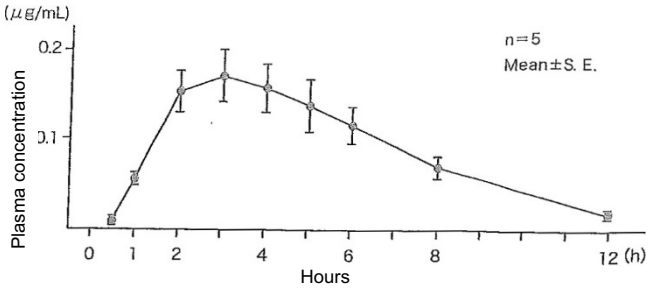
■ Pharmacokinetics ■

1. Absorption[1)]

When a single dose of propagermanium 15mg was administered to healthy adults, it was found that the plasma concentration of the drug peaked at about 3 hr, and the biological half-life was about 2.5 hr.

T_{max}(h)	C_{max}(μg/mL)	$T_{1/2}$(h)	$AUC_{0\to\infty}$(μg · h/mL)
2.8±0.2	0.174±0.029	2.4±0.2	1.17±0.17

(n=5,Mean±S.E.)



2. Metabolism[2,3]

When a single dose of propagermanium 120mg was orally administered to healthy adults, it was confirmed that a structural unit (3-oxygermyl-propionic acid) was not metabolized.

3. Excretion[1]

When a single dose of propagermanium 30mg was orally administered to healthy adults, 41.9% of the drug was excreted into urine within 24 hr and 50.1% of the drug was excreted into feces within 72 hr.

■ Clinical Results ■

Clinical efficacy[4–9]

A double-blind comparison study using placebo as a control was conducted in patients with HBe antigen-positive chronic hepatitis B, and the results indicated that the drug was useful. The efficacy obtained by administering 30 mg of this drug to 249 patients with HBe antigen-positive, chronic hepatitis B in clinical studies, including the double-blind comparison study and general clinical studies, was as follows.

Disease	Effective or greater efficacy	Somewhat effective or greater efficacy
HBe antigen-positive chronic hepatitis B	32.9%(82/249)	62.2%(155/249)

■ Pharmacology ■

1. Action in preventing viral infections (in vivo)

(1) The mortality rate of mice infected with the herpes simplex virus type 2 declined[10].

(2) The number of pox appearing in mice infected with the vaccinia virus was inhibited[11].

2. Immunopotentiation action

(1) Cellular immunity and humoral immunopotentiation action (in vivo)[12–14]

A delayed hypersensitivity reaction in immunodeficient mice and antibody production enhancement effect were observed.

(2) T cell potentiating effect (in vitro)[12, 15, 16]

Action of promoting mouse lymphocytes by conconavalin A (ConA) and action of promoting human lymphocyte transformation reaction by ConA and phytohemagglutinin (PHA-P) were observed.

(3) Inducing activity of cytotoxic T cells (Tc cells)

The induction of mouse allogenic Tc cells and virus specific Tc cells was promoted. Effects in enhancing IL-1 production (in vitro) in (in vivo)[17, 18] mouse and human macrophages as well as IL-2 production (in vitro) in mice and IFN-γ production (in vivo) were observed[15, 17, 19–21].

(4) Effect in activating NK cells (in vivo)[17]

An effect in activating NK cells in mice was observed.

(5) Effect in enhancing IFN production

An effect in enhancing IFN-α/β production in mice infected with the influenza virus was observed (in vivo)[20].

An effect in enhancing IFN production in human peripheral blood lymphocytes infected with the influenza virus was observed (in vitro)[22].

3. Effect on hepatic impairment (in vivo)[23]

In studies using mice or rats, serum transaminase elevation in acute hepatic impairment was inhibited by tetrachloromethane, galactosamine, etc.

4. Mechanism of action

By enhancing the production of IL-1, IL-2 and IFN-γ, etc., propagermanium activates cytotoxic T cells and NK cells and thereby destroys virus infected cells. Moreover, propagermanium stimulates the elimination of viruses associated with antigens by enhancing antibody production. In addition, it inhibits the proliferation of viruses by enhancing IFN-α/β production.

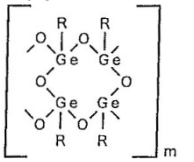
■ Physicochemistry ■

Generic name: Propagermanium

Chemical name: 3-oxygermylpropionic acid polymer

Structural formula: $[(O_{1/2})_3\ GeCH_2CH_2COOH]_n$

Estimated structural formula:



R=CH_2CH_2COOH

Molecular formula: $(C_3H_5GeO_{3.5})_n$

Melting point: Approximately 230°C (decomposition)

Description: Propagermanium is a white, crystalline powder that is odorless and has a slightly acidic taste. It is difficultly soluble in water and practically insoluble in acetone, diethylether, dichloromethane or hexane. It is soluble in 0.02mol/L sodium hydroxide solution.

■ Packaging ■

100 capsules (PTP capsules x 10)

■ References ■

1) Ito M, et al.: Jpn Pharmacol Ther 18: 2231, 1990
2) Sanwa Kagaku Kenkyusho Co., Ltd. In-house document (HPLC analysis of human excreted urine)
3) Sanwa Kagaku Kenkyusho Co., Ltd. In-house document (Analysis of germanium dioxide in human urine)
4) Hirayama C, et al.: Kan Tan Sui (Hepatobiliary and Pancreatic Cancer) 20: 1069, 1990
5) Hirayama C, et al.: The Japanese Journal of Clinical and Experimental Medicine 67: 1227, 1990
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7) Yano U: Jpn J Med Pharm Sci 24: 212, 1990
8) Morizane T, et al.: Jpn J Med Pharm Sci 24: 243, 1990
9) Tsuji H, et al.: The Japanese Journal of Clinical and Experimental Medicine 67: 3219, 1990
10) Fujita H, et al.: Applied Pharmacology 39: 385, 1990
11) Sanwa Kagaku Kenkyusho Co., Ltd. In-house document (Effect on vaccinia virus infection)
※ 12) Ishiwata Y, et al.: Applied Pharmacology 47: 155, 1994
13) Ishiwata Y, et al.: The Clinical Report (Kiso to Rinsho) 24: 301, 1990
14) Sanwa Kagaku Kenkyusho Co., Ltd. In-house document (Effect on antibody production in cancer-carrying mice)
15) Sanwa Kagaku Kenkyusho Co., Ltd. In-house document (Enhancing effect on T cells (1))
16) Sanwa Kagaku Kenkyusho Co., Ltd. In-house document (Enhancing effect on T cells (2))
17) Suzuki E, et al.: The Clinical Report (Kiso to Rinsho) 24: 309, 1990
18) Sanwa Kagaku Kenkyusho Co., Ltd. In-house document
19) Kagami S, et al.: Kan Tan Sui (Hepatobiliary and Pancreatic Cancer) 21: 135, 1990
20) Ishiwata Y, et al.: The Clinical Report (Kiso to Rinsho) 24: 319, 1990
21) Sanwa Kagaku Kenkyusho Co., Ltd. In-house document (Effect on inducing cytotoxic T cells)
22) Sanwa Kagaku Kenkyusho Co., Ltd. In-house document (Enhancing effect on IFN production)
23) Asano K, et al.: The Clinical Report (Kiso to Rinsho) 24: 337, 1990

■ References Contact ■

For in-house documents cited in the References, please contact:

Sanwa Kagaku Kenkyusho Co., Ltd. Contact Center
35, Higashisotoboricho, Higashi-ku, Nagoya 461-8631, Japan
Tel: 0120-19-3810 Fax: (052)950-1305

APPENDIX B – SEROCION ® DRUG PRODUCT INTERVIEW FORM

Created: April 2010 (1st edition)

Japan Standard Commodity Classification No.
873919

Pharmaceutical Interview Form

Prepared according to the Japanese Society of Hospital Pharmacists 2008 IF Drafting Guidelines

Oral Treatment for Chronic Hepatitis B Virus

● **For Prescription Use Only**

SEROCION® Capsule 10

[original English:]

SEROCION® Cap. 10

(propagermanium capsules)

Formulation	Hard capsule formulation
Regulatory Classification	Prescription drug product (Warning—product must be used in accordance with a prescription from a physician or other duly licensed healthcare professional)
Product Specifications/Strength(s)	1 capsule contains 10mg of propagermanium
Generic Name	Japanese name: propagermanium (JAN) English name: propagermanium (JAN, INN)
Manufacturing/Marketing Authorization Date/ NHI Drug Price List Inclusion Date/ Market Debut	Manufacturing/marketing authorization date: July 1, 1994 NHI Drug Price List inclusion date: August 26, 1994 Market debut: August 29, 1994
Product Developer/Manufacturing/ Marketing Authorization Holder (Importer)/ Sales Agent/Distributor	Sanwa Kagaku Kenkyusho Co., Ltd.
Drug Information Supervisor Contact Details	
Contact Details	Contact Center, Sanwa Kagaku Kenkyusho Co., Ltd. TEL: 0120-19-8130 FAX: (052)950-1305 Website for healthcare professionals: http://med.skk-net.com/

This pharmaceutical interview form (IF) was prepared based on the package insert current as of October 2009.

For the most current package insert information for this product, refer to the website of the Pharmaceuticals and Medical Devices Agency (PMDA). http://www.info.pmda.go.jp/

Overview of the Guide to Pharmaceutical Interview Form Use
—The Japanese Society of Hospital Pharmacists—

1. Background of pharmaceutical interview form preparation

The Package Insert for Prescription Drugs (hereinafter, the "package insert") serves as a basic summary of the characteristics, uses, and warnings applicable to a given drug product. However, medical professionals such as doctors and pharmacists sometimes require more detailed information concerning proper drug use than is found in package inserts in their daily practices.

The medical community has addressed this issue by requesting supplemental information concerning specific drug products from drug information supervisors in industry. The pharmaceutical interview form was born from the comprehensive line lists containing the required drug information prepared in response to these requests.

In 1983, the second Academic Subcommittee of the Japanese Society of Hospital Pharmacists (JSHP) established the role of the "Pharmaceutical Interview Form" (IF) and a standardized IF format. In response to subsequent changes in the respective types of drug product information needed by healthcare professionals and patients, the third JSHP Academic Subcommittee revised the IF Drafting Guidelines in September 1998.

Ten years later, in September 2008, the new JSHP Drug Information Council established a new set of IF Drafting Guidelines in response to the substantial changes in the pharmaceutical regulatory affairs and medical environment for both pharmaceutical companies, who are the creators of drug information, and pharmacists, who use this information in practice.

2. What is an IF?

The Pharmaceutical Interview Form (IF) is "a comprehensive collection of technical information prepared by drug manufacturers in accordance with drafting guidelines established by JSHP, based on requests from pharmacists and other healthcare professionals meant to complement the information contained in the package insert of a specific drug product preparation, such as information concerning drug quality control, prescription planning, formulation and compounding, proper use, and drug-based patient care.

However, IFs should not contain items that concern Pharmaceutical Affairs Law compliance, pharmaceutical company confidentiality, undermine or invalidate the manufacturing efforts of pharmaceutical companies, or that must be evaluated, judged, or prepared by healthcare professionals themselves, such as pharmacists. In essence, it is assumed that in addition to medical evaluations, judgments, and clinical measures performed by pharmacists themselves, pharmacists will recognize IFs provided by pharmaceutical companies as supplementary materials to be used as necessary.

[IF Format]

(1) The standard IF format in principle calls for A4 page sizing, horizontal text, and a font sized 9 points or larger (excluding figures), and the IF should be fully viewable with monochrome (black and white) printing. However, if the product's approved package insert includes red text and/or tables, this formatting may be reflected in the electronic version of the IF.

(2) IFs must be created in accordance with the procedure described in the IF Drafting Guidelines, and each section header must be written using a Gothic-style font.

(3) Text on the cover page must be justified, and all body text after the cover page must be formatted in accordance with the "JSHP Guide to IF Use", summarized on page 2.

[IF Creation]

(1) In principle, an IF is prepared for each route of administration (oral use, for injection, for topical use, etc.) of the drug product in question.

(2) The items and lists described in the IF shall be in conformity with the JSHP IF Drafting Guidelines.

(3) The IF's main purpose is to provide the information necessary to supplement the contents of drug package inserts.

(4) IFs should not contain items that concern the confidentiality of pharmaceutical companies, undermine or invalidate the manufacturing efforts of pharmaceutical companies, or that must be evaluated, judged, or prepared by healthcare professionals themselves, such as pharmacists.

(5) IFs prepared in accordance with the "2008 Pharmaceutical Interview Form Drafting Guidelines" (hereinafter, "2008 IF Drafting Guidelines") will generally be disseminated in electronic form, and pharmacists may print the electronic IF (PDF, etc.) as necessary.

[IF Publication]

(1) The "2008 IF Drafting Guidelines" will apply to IFs prepared for drugs approved after April 2009.

(2) Adherence to the "2008 IF Drafting Guidelines" is not required when creating/distributing IFs for drug products other than those mentioned above.

(3) IFs are revised when usage warnings are amended, reexamination results (clinical reassessment) are announced, when there is an expansion of indications, or any other major change to the items required to be included in the IF.

3. Using IFs

IFs prepared in accordance with the "2008 IF Drafting Guidelines" will generally be disseminated in electronic form, and pharmacists may in principle print the electronic IF (PDF, etc.) as necessary, and depending on the IT environment at his or her affiliated medical institution, pharmacists may request hard copies of the IF from the corresponding medical representative (MR).

IFs in electronic format are made available on a designated section of the Medical Product Information Website of the Pharmaceuticals and Medical Devices Agency (PMDA).

Although pharmaceutical manufacturers prepare and distribute IFs in accordance with the "Guidelines for Preparing Pharmaceutical Interview Forms", depending on the subject of the IF, it may be necessary for information that is lacking in actual medical practice or that is difficult to describe when preparing the IF to be provided by industry MRs in order to increase the usability of the IF. In addition, with respect to items related to usage warnings that are occasionally revised, until the IF is revised, until such revisions are published, pharmacists should refer to the most current package insert information available on the PMDA Medical Product Information Website in addition to their own efforts to gather information pertinent to the drug in question through its labeling information, related regulatory notifications, and services such as the Pharmaceuticals and Medical Devices Information E-mail Alert Service (PMDA Medi-navi).

In addition, described from the perspective of proper use and safety assurance such as "clinical performance" and "Sales conditions in major overseas markets" related to product approval should be considered carefully.

4. Points to consider regarding IF use

IFs should be used as a source of drug information essential to the daily operations of pharmacists and other healthcare professionals. However, the amount and scope of product information that manufacturers can provide is of course limited by regulations under the Pharmaceutical Affairs Law and by industry standards such as the Japan Pharmaceutical Manufacturers' Association (JPMA) Promotion Code for Prescription Drugs. Because IFs are prepared and disseminated by the manufacturer of the drug product in question based on the IF Drafting Guidelines, users should be advised that the information and language used are limited to the constraints of these Guidelines. Pharmaceutical manufacturers should also recognize that IFs ultimately are a supplementary information source meant to accompany a given product's approved package insert. As publication via the Internet increases in the future, manufacturers must ensure that IFs they create are compliant with applicable advertising and promotion restrictions under the Pharmaceutical Affairs Law.

(September 2008)

Table of Contents

I. Overview

1. Developmental background

The use of organic germanium compounds in pharmaceutical products was first devised in the 1960s. Ryuichi Sato, et al. focused their research on organic germanium compounds capable of enhancing cellular immunity and in 1978, they synthesized propagermanium, a novel organic germanium compound.

Nonclinical study results indicated that propagermanium exhibits protective effects against viral infection arising from its immunostimulatory action, and no toxicological issues were identified. In clinical trials, propagermanium was found to generally improve chronic hepatitis B symptoms and all effects were confirmed to be significantly superior to placebo. Sanwa Kagaku Kenkyusho Co., Ltd. applied for Japanese manufacturing and marketing authorization for this compound under the brand name Serocion® capsules 10 on August 30, 1990, obtained approval on July 1, 1994, and began sales on August 29, 1994.

As a result of applying for reexamination on September 29, 2000, the company was informed (summary basis for approval/rejection) that propagermanium no longer fell within the scope of Article 14, Paragraph 2 of the Pharmaceutical Affairs Law on November 26, 2003.

2. Therapeutic and pharmaceutical properties

(1) Propagermanium is a drug indicated for the treatment of chronic hepatitis B (HB).
   1) Propagermanium is expected to suppress HB viral proliferation by increasing interferon (IFN) production.
   2) Propagermanium is expected to promote viral clearance by enhancing immune functions.

(2) Propagermanium is effective in improving viral markers.
Propagermanium is expected to improve viral markers such as HBe antibodies and HBe antigens.

(3) Propagermanium is easily taken orally, and is useful in treating outpatients.
Propagermanium is an oral drug developed in consideration of the quality of life (QOL) of chronic HB patients.

(4) Adverse reaction onset rate at the time of approval was 6.56% (49/747 subjects), and was 13.56% (172/1268 cases) in the use performance evaluation. The most frequently occurring adverse reactions were as follows: elevated AST(GOT): 38 subjects (1.89%), elevated ALT(GPT): 40 subjects (1.99%), languor: 27 subjects (1.34%), and decreased appetite: 18 subjects (0.89%).
Exacerbation of chronic HB to acute HB was reported as a severe adverse reaction. (See adverse reaction-related sections in VIII. 8. Safety)

II. Product name-related items

1. Proprietary name

(1) Japanese name: SEROCION® Capsule 10

(2) English name: SEROCION® Cap.10

(3) Name origin: SERO=blood (blood/serum)
CION= “Scion” (seedling)
These name components are placed before and after an abbreviated “seroconversion” to become “SEROCION”.

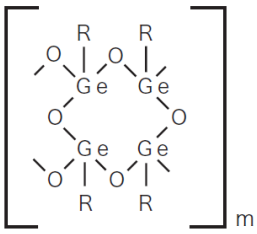
2. Generic name

(1) Japanese name (nomenclature): Propagermanium (JAN)

(2) English name (nomenclature): Propagermanium (JAN, INN)

(3) Stem: other compounds “-ium”

3. Structural formula or rational formula



$R=CH_2CH_2COOH$

4. Molecular formula and weight

Molecular formula: $(C_3H_5GeO_{3.5})_n$

Molecular weight: $(9.29\pm5.72)\times10^4$ (average molecular weight converted from the molecular weight of propagermanium propyl ester)

5. Chemical name (nomenclature)

3-oxygermylpropionic acid polymer (IUPAC)

6. Common name, alt. name(s), abbreviations, code number

SK-818 (clinical trial number)

7. CAS registration number

12758-40-6

III. Active ingredient

1. Physicochemical properties

(1) External appearance/characteristics

Propagermanium contained in this product takes the form of a white-colored, odorless, slightly sour-tasting crystalline powder.

(2) Dissolution

Solvent name	Amount of solvent needed to dissolve 1g of product	Solvency
Water	≥100mL ≤1000mL	Low solvency
Ethanol (95)	≥10000mL	Almost insolvent
Acetone	≥10000mL	Almost insolvent
Diethylether	≥10000mL	Almost insolvent
Dichloromethane	≥10000mL	Almost insolvent
Hexane	≥10000mL	Almost insolvent

Dissolves in a 0.02mol/L sodium hydroxide solution.

(3) Hygroscopicity

No significant hygroscopicity was observed as volume changes were 1.0% or lower after storing this product for 8 days at 38°C in 50, 61, 75, 79, 85, 91%RH.

(4) Melting point (decomposition point); boiling point; freezing point

Melting point: approximately 230°C (decomposition)

(5) Acid-base dissociation constant

pKa: 4.16

(6) Distribution coefficient

Measurement temperature: 37°C

pH	1.0	4.0	9.0
P	1.047×10^{-2}	*	*

* No propagermanium was detected in the n-octal layer.

(7) Other major rational values

pH: 2.94–2.96 (20°C, 0.5% aqueous solution)

2. Active ingredient stability under various conditions

(1) Solid-state stability

Test item		Storage conditions	Storage period	Storage method	Test result
Long-term storage testing[1)]		Room temperature	39 months	Clear glass vials (sealed)	No change
Accelerated testing[2)]		Room temperature	6 months		
		40°C, 75%RH			
Stress testing[2)]	Temperature	40°C	12 months		
		50°C			
		60°C			
	Humidity	38°C, 100%RH	28 days	Open containers	Changes were observed from day 7, and changes ceased by day 28; decomposition products were observed
		38°C, 91%RH			No change
		38°C, 75%RH			
		38°C, 50%RH			
		30°C, 100%RH			Decomposition products were observed by day 28
		20°C, 100%RH			
	Light	Xenon fade meter	3 days	Quartz Petri dishes (sealed)	No change
		Indoor scattered light	6 months		

Measurement items: Physical properties, identification, purity testing, volume loss due to dehydration, strength

(2) Stability in aqueous solution [4)]

Propagermanium was prepared to 1% concentration and stored in the following solvents.

Solvent	Irradiation conditions	Storage conditions	Storage period	Results
Water	10,000Lux	40°C	3 days	No change
0.1N HCl	10,000Lux	40°C	3 days	No change
0.1N Sodium hydroxide	10,000Lux	40°C	3 days	No change

Measurement item: HPLC

3. Active ingredient test method

(1) Color reactions (1)

(2) Color reactions (2)

(3) Infrared absorption spectrum

4. Active ingredient quantification method

(1) Neutral titer

(2) Atomic absorption photometric method

IV. Product formulation

1. Dosage form

(1) Preparation classification, specifications, and physical properties

1) Classification: hard capsule preparation

2) Properties: Serocion 10 is sold as a white-capped, white-bodied No. 4 hard capsule.

Propagermanium contained in this product takes the form of a white-colored, odorless, slightly sour-tasting crystalline powder.

3) Specifications:

	Cap	Body
External Appearance		
	White	White
ID Code	Weight (contents)mg	
Sc281	220(180)	

(2) Drug physical properties

No applicable materials.

(3) Identification code

Sc281

(4) pH, osmotic pressure ratio, viscosity, specific gravity, sterility, and stable pH range

Not applicable.

2. Formulation composition

(1) Active ingredient strength

One capsule contains 10mg of propagermanium

(2) Additives

Active ingredient: Hydroxypropyl cellulose, Mg stearate, lactose hydrate

Capsule body: Sodium lauryl sulfate

(3) Other items

Nothing noteworthy.

3. Warnings concerning dissolutive capacity of suspensions and emulsions

Not applicable.

4. Formulation stability under various conditions

Test item		Storage conditions	Storage period	Storage method	Test result
Long-term storage testing[5)]		Room temp.	39 months	PTP+ aluminum foil wrapping	No change
Accelerated testing[6)]		Room temp.	6 months	PTP+ aluminum foil wrapping	
		40°C, 75%RH			
Stress testing[7)]	Temp.	50°C	4 months	PTP+ aluminum foil wrapping	
	Humidity	40°C, 75%RH	180 days	Open containers	1.5–1.9% decomposition at day 15 and 14.2–23.5% decomposition at day 180 was observed. The product produced a distinct odor as well as discoloration and deformation as it decomposed.
	Light	Xenon fade meter	3 days	Quartz Petri dishes (sealed)	No change

Measurement items: Physical properties, confirmation testing, purity testing, weight deviation testing, disintegration testing, strength

5. Method of preparation and stability after dissolution

Not applicable.

6. Changes due to compounding with other substances (physicochemical changes)

Not applicable.

7. Elutive properties

8. Biological test methods

Not applicable.

9. Method of confirming active ingredient presence in product preparation

(1) Color reactions (1)

(2) Color reactions (2)

(3) Infrared absorption spectrum

10. Quantification of active ingredient in product preparation

Atomic absorption photometric method.

11. Titer

Not applicable.

12. Potential contaminants

Propegermanium decomposition products (D-1)

Molecular formula: $(C_3H_5GeO_{3.5})_n$: 169.71 × n n is an integer equal to 2 or more.

13. Information concerning containers requiring special treatment

No applicable materials.

14. Other items

None.

V. Treatment-related items

1. Effects and efficacy

Propagermanium acts to improve virus markers associated with HBe antigen-positive chronic hepatitis B.

2. Dose and dosing method

30mg of propagermanium was orally administered postprandially three times each day to healthy adults.

<Dose/dosing method-related warnings>
Clinical laboratory tests including viral markers (such as HBe antigens) should be conducted at 16 weeks after administration, and if no improvement in viral markers is observed, other therapies should be considered.

3. Clinical performance

(1) Clinical data package (product approved as of April 2009)

Not applicable.

(2) Clinical effects [8-13)]

The efficacy of propagermanium was confirmed based on the results of a double-blind comparative study against placebo in patients presenting with HBe antigen-positive chronic hepatitis B. The efficacy rate of HBe antigen-positive chronic hepatitis B in 249 subjects in clinical trials including both double-blind comparative studies and general clinical trials investigating 30mg of propagermanium is as follows:

Disease name	Favorable efficacy	Somewhat favorable efficacy
HBe antigen-positive chronic hepatitis B	32.9% (82/249)	62.2% (155/249)

(3) Clinical pharmacological testing: tolerability assessment

1) Single-dose study[14)]

Five healthy adult men were given single doses of propagermanium of 15mg, 30mg, 60mg, 120mg, and 240mg on an empty stomach, and another 30mg single dose after meals. No abnormalities believed to be caused by propagermanium were observed following examination for subjective symptoms, auscultation, physiological symptoms, and clinical laboratory tests (electrocardiogram, blood biochemistry, hematology, endocrine, urinalysis).

14) Ito K, et al: Japanese Pharmacology & Therapeutics, 18(6): 2231, 1990.

2) Repeated-dose study[15)]

No abnormalities believed to be caused by propagermanium were observed following examination for subjective symptoms, auscultation, physiological symptoms, and clinical laboratory tests as a result of postprandial administration of 60mg of propagermanium to five healthy adult men three times daily over a 7-day period.

15) Ito K, et al.: Japanese Pharmacology & Therapeutics, 18(7):2631, 1990.

Note: The approved dose and dosing method for this product is “In healthy adults, 30mg of propagermanium taken orally after every meal three times daily.”

(4) Exploratory study: dose-response study[8)]

One-hundred-twenty-one patients presenting with chronic hepatitis B were divided into three groups receiving 30mg/day, 60 mg/day, or 90 mg/day of propagermanium over a 12-week period, and clinical utility, optimal dosage, and safety were evaluated. As a result, by week 12, patients in the 30mg/day group exhibited significant improvement in GOT, ALP, and γ-GTP levels as well as significant improvement in the severity of liver function test items including significantly decreased GOT, GPT, and HBe antigen levels. Better than marginal utility was observed more frequently in the 30mg/day group compared with the other groups, and 30mg/day was determined to be the optimal dose. No severe adverse reactions were observed.

8) Hirayama C, et al.: The Journal of Hepato-Biliary-Pancreatic Sciences, 20(6): 1069, 1990.

Note: The approved dose and dosing method for this product is "In healthy adults, 30mg of propagermanium taken orally after every meal three times daily."

(5) Validation testing

1) Randomized parallel dose-response study[9)]

Seventy-eight patients presenting with chronic hepatitis B, were given 15mg/day or 30mg/day of propagermanium over a 12-week period as part of a double-blind study to evaluate clinical utility, optimal dosage, and safety. As a result, in patients in the 30mg/day group exhibited improved liver function and clinical utility tended to be superior in comparison to the 15mg/day group. Patients in the 30mg/day group exhibited significant decreases in GOT and GPT levels, and superior rates of decline in HBe antigen levels were also observed. Accordingly, 30mg/day was determined to be the optimal dose. No severe adverse reactions were observed.

9) Hirayama C, et al.: The Japanese Journal of Clinical and Experimental Medicine, 67(4): 1227, 1990.

Note: The approved dose and dosing method for this product is "In healthy adults, 30mg of propagermanium taken orally after every meal three times daily."

2) Comparative study[10)]

One-hundred-one patients presenting with chronic hepatitis B were given 30mg/day of propagermanium 30mg/day and 81 patients were given a placebo over a 16-week period as part of a double-blind study. As a result, subjects in the propagermanium group exhibited significantly superior improvement in liver function as well as overall improvement compared with the placebo group. As a result of comparing liver functions after 16 weeks, patients in the propagermumumium group exhibited significant improvements in GPT, total cholesterol, GOT, and γ-globulin levels in comparison with the placebo group. In addition, propagermanium group patients exhibited significantly superior HBe antigen and HBe antibody levels in comparison with the placebo group. Propagermanium is effective for improving chronic hepatitis B symptoms, and is believed to be a highly useful therapeutic agent. Observed adverse reactions were minor.

10) Hirayama C, et al.: Journal of Clinical and Experimental Medicine, 154(10): 663, 1990.

3) Safety testing[11)]

10mg of propagermanium was given to 34 patients presenting with chronic hepatitis B three times daily over a 1-year period, and efficacy and safety were assessed using liver histological images and liver function test results as indices. As a result, significant decreases in GOT and GPT levels were observed 16 weeks after administration. Adverse reactions occurred in 1 patient (skin eruption, itching, general languor), but were not serious. These results suggest that propagemanium is safe even when administered long-term.

11) Yano T, et al.: Japanese Journal of Medicine and Pharmaceutical Science, 24(1): 212, 1990.

4) Patient/disease testing

No applicable materials.

(6) Therapeutic use

1) Usage performance examination / Specific use examination (special examination) / Post-marketing clinical trial

Usage performance examination/special examination implementation status

No applicable materials (SBR had not yet been created)

2) Summary of planned or completed clinical studies conducted as a requirement for product approval

Not applicable.

VI. Pharmacodynamics

1. Pharmacologically-related compounds or pharmacological class members

Interferon alfacon 1 (genetical recombination)
Interferon alpha
Interferon alpha 2b (genetical recombination)
Interferon beta
PEG-interferon alpha 2a (genetical recombination)
PEG-interferon alpha 2b (genetical recombination)

2. Pharmacodynamic effects

(1) Effect site/effect mechanism

Effect site: Liver

Effect mechanism: Propagermanium activates cytotoxic T-cells and NK cells by enhancing production of cytokines such as IL-1, IL-2, and IFN-γ, which destroy virus-infected cells. In addition, this product promotes virus-related antigen clearance by enhancing antibody production. Furthermore, this product suppresses viral proliferation by enhancing IFN-α/β production.

(2) Study performance supportive of product efficacy

1) Antiviral effects (*in vivo*)

(1) *I*n vitro antiviral effects[16)]

The antiviral activity of propagermanium was determined based on a CPE (cytopathogenic effect) inhibition test conducted on DNA and RNA viruses. Propagermanium did not inhibit CPE.

(2) Effect on Herpes simplex virus type II-infected mice[16)]

The antiviral activity of propagermanium was investigated in mice infected with herpes simplex virus type II. As a result, suppression of viral infection and significantly extended survival time was observed.

(3) Effect on vaccinia virus infection[17)]

As a result of measuring the protective effects of propagermanium in vaccinia virus-infected mice, significant suppression of pocks formed on the tail of each mouse was observed after administering 1mg/kg and 10mg/kg.

Drug	Dose	No. of pocks
Control group		16.5±2.2
Propagermanium	1.0mg/kg	5.6±1.0***
	10.0mg/kg	7.8±1.7**

Each value represents the mean ± standard error for a group of 9–10 animals.
**p <0.01, ***p<0.001 (t-test)

2) Immune activation effects

(1) Cellular immunity and humoral immunostimulatory action (*in vivo*)[18-20)]

a) Delayed-type hypersensitivity reaction in mice with immune disorders

The immune activation effects of propagermumium were studied in tumor-bearing mice and mice treated with hydrocortisone serving as immunocompromised model mice exhibiting DTH reactions using SRBC as an antigen and index. As a result, reduction of DTH responses in tumor-bearing mice was significantly recovered by pre-administration and continuous administration. In addition, DTH response decreased as a result of hydrocortisone treatment was also significantly restored.

b) Enhancement of antibody production in mice with immune degradation

The immunological effects of propagermanium were assessed in tumor-bearing mice and mice treated with hydrocortisone using the number of antibody-producing cells (PFC count) and SRBC as an antigen. As a result of propagermanium administration, the decrease in splenocyte PFC count in both the tumor-bearing mice and hydrocortisone-treated mice recovered to normal levels.

(2) T-cell activation effect (*in vitro*)[18,21,22)]

a) Mouse lymphocyte recruitment response

Splenocytes in mice were suspended in a culture medium containing 0.1–100μg/mL of propagermanium and ConA was added as a T-cell mitogen or LPS as a B-cell mitogen. Progermanium alone did not induce blastogenesis, and recruitment induced by LPS also did not induce blastogenesis, but the addition of ConA significantly increased blastogenesis. 6.3μg/mL was found to be the optimal propagermanium dosage. Based on these results, it was confirmed that propagermanium acts on T-cells and has immunostimulatory effects.

b) Human peripheral blood lymphocyte blastogenesis

0.047–100μg/mL of propagermanium was added to a culture medium containing human peripheral blood lymphocytes as well as ConA or PHA-P. As a result of incubation, a significant recruitment response-promoting effect was observed with propagermanium concentrations of 2.2–10μg/mL even in the presence of PHA-P. These findings demonstrated that propagermanium significantly enhances human peripheral blood lymphocyte recruitment responses in the presence of any mitogen.

(3) Inductive effect on cytotoxic T-cells (Tc cells)

a) Effect on Tc cell induction

Tc cells with the same alloantigen and EL-4 tumor cells were combined and simultaneously transplanted into the abdominal cavity of mice, and the extent of Tc cell induction was measured based on the number of days of survival. As a result, the average survival period in days in the non-administration group was 17.0 ± 0.27 days, and a prolonging effect resulting in a survival period of 17.6 ± 0.38 days in the 1mg/kg propagermanium group, 18.1 ± 0.35 days in the 10mg/kg group, and 17.5 ± 0.27 days in the 100mg/kg group. These findings suggested that propagermanium has an Tc cell induction-enhancing effect[23)]. As a result of intraperitoneally inoculating mice with herpes simplex virus type 1 (HSV-1) and subsequently measuring HSV-1-specific Tc cell activity, activity was observed on day 6 from 0.2mg/kg in the propagermanium group, and a significant increase in Tc cell activity was observed with doses up to 10mg/kg, with peak activity observed with 1mg/kg[24)].

b) Effects on IL-1, IL-2, and IFN production and IL2R expression

Mouse intraperitoneal macrophages were cultured in a medium containing propagermanium, and the amount of IL-1 present the culture supernatant was measured. As a result, increased IL-1 production was confirmed[23].

It was not until indomethacin was added during the human macrophage culture and the suppressor effect of the macrophages was removed that the IL-1 production-enhancing effect of propagermanium was observed. A similar effect was also confirmed with respect to IL-2 production by human T-cells[25].

Propagermanium at concentrations of 0.1–100μg/mL were added to mouse splenocytes in the presence of ConA (1.6μg/mL), then cultured for 24 hours, and the culture supernatant was collected. As a result of measuring IL-2 activity, propagermanium alone had no effect on IL-2 production, but significantly enhanced IL-2 production in the wide dose range of 0.1–100μg/mL in the presence of ConA[21].

As a result of measuring IFN-r activity in BCG-sensitized mice following oral administration of propagermanium, IFN-r activity was 129IU/mL in the control group, and in the propagermanium group, a 3.7-fold increase was observed in mice given 1mg/kg and a 5-fold increase was observed in the mice given 10mg/kg, demonstrating a significant increase in IFN-r activity[26].

Assessment of the effect of propagermanium on lymphocyte subset variation in an *in vitro* anti-SRBC antibody production test model using mouse splenocytes revealed that the ratio of IL-2R positive cells to 1μg/mL and 10μg/mL doses of propagermanium was 1.28-fold and 1.16-fold in comparison to the control group. These increases suggest that propagermanium acts on the immune system by enhancing lymphocyte IL-2R expression[27].

(4) Activation effect on natural killer (NK) cells (*in vivo*)[23]

Mice were given 0.1, 1, 10, and 100mg/kg single doses of propagermanium, and NK cell activity was measured 24 hours later. As a result, increased NK cells activity was confirmed.

NK cell activity was also measured by preparing mouse splenocytes, incubating them in a culture medium, and then adding various concentrations of propagermanium or Poly I:C. As a result, no NK cell activity was detected at any concentration, but NK activity was observed depending on the concentration of Poly I:C, which directly acts on NK cells to cause activation. As such, these findings suggest that propagermanium does not directly activate NK cells.

(5) Enhancing effect on IFN production

Mice were intratracheally inoculated with influenza virus and propagermanium was administered immediately afterward. As a result, IFN activity in the lung homogenate centrifugal supernatant and serum appeared to be enhanced. IFN-α/β production was enhanced in the lungs[26].

Testing of the enhancing effect on IFN production by human peripheral blood monocytes infected with influenza virus revealed that the action takes effect at 2μg/mL and the effect reached the target level at 5–10μg/mL[28].

3) Effects on liver damage during testing[29]

Continuous oral administration of 1–10mg/kg of propagermanium over a 5-day period to address hepatopathy induced by hepatotoxic compounds such as carbon tetrachloride (mice), D-galactosamine (rats), and l-naphtylisothiocyanate (mice), resulted in suppressed elevation of serum transaminase in all cases.

(3) Time until effect manifestation/activation period

No applicable materials.

VII. Pharmacokinetics

1. Shifts in blood concentration/measurement method

(1) Therapeutic blood concentration

No applicable materials.

(2) Time to peak blood concentration

Approximately 3 hours.

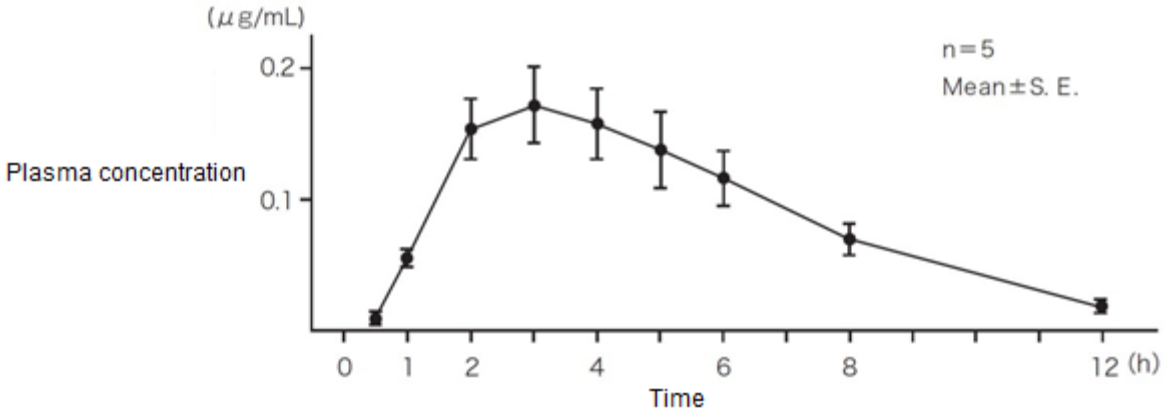
(3) Blood concentrations confirmed in clinical trials

1) Single dose[14)]

As a result of orally administering 15mg of propagermanium to healthy adult men, peak blood concentration was reached after approximately 3 hours, and biological half-life was reached after approximately 2.5 hours.

T_{max} (h)	C_{max} (μg/mL)	$T_{1/2}$ (h)	$AUC_{0\rightarrow\infty}$ (μg•h/mL)
2.8±0.2	0.174±0.029	2.4±0.2	1.17±0.17

(n=5, Mean±S.E.)



Note: The approved dose and dosing method for this product is “In healthy adults, 30mg of propagermanium taken orally after every meal three times daily.”

2) Repeated dosing[15)]

Although plasma concentrations were somewhat low on days 2, 3, and 5 after 60 mg of propagermanium was continuously orally administered postprandially 3 times daily to healthy adult men for 1 week, all subjects exhibited similar plasma concentrations on day 7.

Note: The approved dose and dosing method for this product is “In healthy adults, 30mg of propagermanium taken orally after every meal three times daily.”

(4) Toxic range

No applicable materials.

(5) Food/drug interactions [14)]

As a result of measuring the pharmacokinetic parameters in healthy adult men given 15mg and 30mg of propagermanium without food, the AUC and C_{max} of postprandially administered propagermanium were approximately 1/2 the values reached without food.

Dose amount		T_{max} (h)	C_{max} (μg/mL)	$AUC_{0\rightarrow\infty}$ (h•μg/mL)	Kel (h^{-1})	$T_{1/2}$ (h)	Urinary excretion rate (%)
15mg	Fasted	2.8±0.2	0.174±0.029	1.17±0.17	0.301 ±0.022	2.4±0.20	52.9±7.3
30mg	Fasted	3.2±0.2	0.269 ±0.031	1.77±0.17	0.290 ±0.008	2.40±0.07	41.9±3.7
	Postprandially	3.8±0.2	0.137 ±0.009	0.838 ±0.060	0.317 ±0.009	2.19±0.06	20.7±1.9

(n=5, mean±SE)

Urinary excretion rate is 0-24h

(6) Changes in *in vitro* pharmacodynamics properties identified through population analysis

No applicable materials.

2. Pharmacokinetic parameters

(1) Compartment model

No applicable materials.

(2) Absorption rate constant

No applicable materials.

(3) Bioavailability

No applicable materials.

(4) Excretion rate constant[14)]

Kel(h^{-1}) = 0.290±0.008 (in 5 healthy adult men orally administered 30mg of propagermanium while fasted)

(5) Clearance

No applicable materials.

(6) Volume of distribution

No applicable materials.

(7) Plasma protein binding rate[30)]

4% human serum albumin (*in vitro*): 0.6–6.9%

3. Absorption

No applicable materials.

<Reference: animal test data – rats>[31)]

As a result of absorption tests targeting the stomach, duodenum, small intestine (upper part, lower part), cecum, and colon of male rats applying the ligation loop method, the absorption rates of propagermanium after 1 hour were uniformly approximately 10%, with the exception of the cecum, and no differences in absorption rates or specific absorption sites were identified.

Absorption site	Propagermanium absorption rate (% of dose)	
	1h	3h
Stomach	9.8±2.4 (5)	
Duodenum	11.3±1.7 (5)	13.9±3.4 (6)
Upper small intestine	8.4±2.6 (4)	12.9±2.0 (6)
Lower small intestine	10.4±1.2 (5)	12.3±3.4 (5)
Cecum	1.4±0.7 (5)	3.4±1.0 (5)
Rectum	6.6±0.5 (5)	5.9±2.9 (5)

( ): n, mean±S.E.

4. Distribution

(1) Blood-brain barrier permeability

No applicable materials.

<Reference: animal test data – rats>[32)]

As a result of measuring whole body radiation in fasted male rats orally administered 5mg/kg of ^{14}C-propagermanium, central nervous system radiation was the lowest overall, whole body radiation was low 6 hours after administration, and no radioactivity was observed in any tissues 120 hours after administration. However, while almost no radiation was detected in male rats intravenously administered 1.5mg/kg of ^{14}C-propagermanium based on a whole body autoradiogram, central nervous system radiation was extremely low. It can be inferred from this result that propagermanium has low blood-brain barrier permeability.

(2) Blood-placental barrier permeability

No applicable materials.

<Reference: animal test data – rats>[33)]

Fetal radioactivity at 2 hours after administration of a single 5mg/kg dose of ^{14}C-propagermanium was administered to pregnant rats was lower than the level of radioactivity observed in maternal blood on gestational days 12 and 18, and drug mobility was low.

(3) Entry into breast milk

No applicable materials.

<Reference: animal test data – rats>[33)]

Radioactivity in milk as a result of oral administration of 5mg/kg of ^{14}C-propagermanium to lactating rats increased to nearly peak levels 4 hours after administration, and concentration of the drug in milk was approximately the same as in the blood. Milk concentration was minimal after the drug was no longer present in the blood, and findings suggested that the concentration falls below the quantity limit over 96 hours with no residual concentration.

(4) Mobility to cerebrospinal fluid

No applicable materials.

(5) Mobility to other tissues

No applicable materials.

<Reference: animal test data – rats>[32)]

As a result of assessing tissue distribution following oral administration of single 5mg/kg doses of ^{14}C-propagermanium to male rats, high radioactivity was observed in the gastrointestinal tract and its contents, as well as in the bladder, kidney and liver, but migration to other tissues was minimal. Propagemanium was confirmed to have been excreted from the body without remaining in specific tissues at 120 hours after administration, defined as a maximum concentration of 10% or lower or a level below the detection limit. Concentration in all tissues tended to maintain a constant level after 14 doses as a result of repeated oral administration of 5mg/kg of ^{14}C-propagermanium to male rats. The highest tissue concentration after 21 doses was observed 1.5 hours after administration in most tissues and decreased after 120 hours with no long-term residual tendencies.

5. Metabolism

(1) Metabolic sites and pathways

No applicable materials.

<Reference: animal test data – rats>[31)]

No further metabolic transformation past 3-oxygermylpropionic acid, the molecular skeletal base of the unmetabolized propagermanium molecule, was detected following oral administration of 25mg/kg of ^{14}C-propagermanium to male rats, based on the behavior of Ge in the blood as well as urinary and expiratory excretion.

(2) Molecules affecting metabolic enzymes (CYP450, etc.)

No applicable materials.

<Reference: animal test data – rats>[34)]

No significant differences in comparison with the control group were observed as a result of measuring liver weight, and cytochrome P-450 and aminopyrine N-demethylase activity (n=24) in rats administered single 1.0mg/kg or 100mg/kg doses of propagermanium once daily over a 7-day period. These findings suggested that propagermanium has no enzyme-inducing effects.

(3) Presence of the first-pass effect and corresponding metabolic rate

No applicable materials.

(4) Metabolite presence and production ratio

Not applicable.

(5) Pharmacokinetic parameters of active metabolites

Not applicable.

6. Excretion

(1) Excretion sites and pathways[14)]

Urine, stool.

(2) Excretion rate

The urinary excretion rate (0-24 hours) exhibited by 5 healthy adult men given single 30mg doses of propagermanium was 41.9 ± 3.7% while in a fasted state and 20.7 ± 1.9% postprandially. In contrast, the rate of excretion in stool (0-72 hours) was 50.1 ± 7.4% [14)].

<Reference: animal test data – rats>[31)]

As a result of oral or intravenous administration of ^{14}C-propagermanium to male rats, the biliary excretion rate after intravenous administration was approximately equal to the fecal excretion rate in stool, and findings suggested that propagermanium is not circulated through the intestines even when it is excreted in bile.

(3) Excretion speed

No applicable materials.

7. Rate of removal by dialysis

No applicable materials.

VIII. Safety (usage warnings)

1. Warning details and rationales

Acute exacerbation of chronic hepatitis and patient death have been reported with respect to use of this product.

2. Contraindications and rationales (generally contraindicated substances)

(1) Patients with jaundice [chronic hepatitis B may become severe.]
(2) Patients with actual or suspected liver cirrhosis [chronic hepatitis B may become severe.]
(3) Patients with a history of hypersensitivity to this product

3. Usage warnings related to product effects or efficacy and rationales

Not applicable.

4. Usage warnings related to product dosage or dosing method and rationales

Refer to "V. Treatment-related items".

5. Careful use guidance and rationale

(1) Patients with a history of drug hypersensitivity
(2) Patients with severe renal impairment [This product is mainly excreted via the kidneys and elevation to unsafe high blood concentrations have been reported in renal dysfunction model rats (single nephrectomy).]
(3) Patients with a history of jaundice [acute exacerbations of chronic hepatitis B may occur.]
(4) Patients who recently received an interferon preparation [increase in viral load and deterioration of liver functions may occur after completion of interferon therapy.]
(5) Elderly patients [see 9. Use in the elderly]

6. Important general warnings and rationales/treatment methods

(1) When using this product, confirm that the patient is **positive for HBe antigens**. In addition, measure transaminase, albumin, coagulation factor, and thrombocyte levels, and confirm the patient's condition as **non-cirrhotic chronic hepatitis** before use.
(2) As **acute exacerbation of chronic hepatitis B** may occur, please consider the following:
1) Upon initiating use of this product
HBV-DNA (or DNA-P) should be measured when administering this product (or DNA-P) to confirm that viral load is not significantly increased (acute exacerbation of chronic hepatitis B can occur in conjunction with increased HBV viral load during the natural disease course.)
2) During administration of this drug
(1) Periodically measure HBV-DNA (or DNA-P), and if a significant increase is observed, discontinue use of this product and consider alternative therapies (acute exacerbation of chronic hepatitis B can occur in conjunction with marked increases in HBV-DNA (or DNA-P).)
(2) **Periodically** assess **liver functions (particularly at weeks 2, 4 and 6 after initiating use.)**
(3) If **exacerbation** of **liver function disorder**, **jaundice**, or other abnormalities are observed,

discontinue use immediately and take appropriate countermeasures.

(4) Instruct patient to notify prescriber immediately if he/she experienced yellowing of the skin/eyes or hemosiderinuria.

(3) In order to properly investigate clinical efficacy of this product, please consider the following:

1) Conduct laboratory testing every four weeks during the treatment period (Liver functions should be assessed at weeks 2, 4 and 6 after initiating use [see previous section].)

2) If the patient became negative for HBe antigen, discontinue use.

7. Interactive effects

(1) Counterindications and rationales

Not applicable.

(2) Concomitant use warnings and rationales

Not applicable.

8. Adverse reactions

(1) Overview of adverse reactions

Of a total of 2,015 patients, adverse reactions were reported in 221 patients (10.97%). The main symptoms were as follows: elevated AST (GOT): 38 (1.89%); elevated ALT (GPT): 40 (1.99%); general languor: 27 (1.34%); diminished appetite: 18 (0.89%). [At completion of re-examination]

(2) Major adverse reactions and initial symptoms

Acute exacerbation of chronic hepatitis B:

As severe liver dysfunction accompanied by jaundice and marked transaminase elevation as well as liver failure may occur, periodic (particularly at weeks 2, 4 and 6 after initiating use) liver function assessment is recommended. If abnormalities are observed, discontinue use immediately and take appropriate countermeasures.

(3) Other adverse reactions

	<0.1-5%	<0.1%
Hypersensitivity[Note 1)]	Skin rash, itching, urticaria	Eczema
Gastrointestinal	Reduced appetite, stomach pain, nausea, emesis, diarrhea, loose stool, abdominal bloating, heartburn, dry mouth	Stomach fullness (sensation)
Nervous system	Depression[Note 1)], drowsiness, vertigo, headache, numbness of fingers	Insomnia, tremors
Liver[Note 2)]	Jaundice, AST (GOT) elevation, ALT (GPT) elevation, elevated bilirubin	
Blood[Note 1)]	Eosinophilia	Leukopenia
Other	Menstrual disorders, hair loss, fatigue, increased blood pressure	Fever, arthralgia, chest pain, edema

Note 1) If symptoms appear, discontinue administration immediately and take appropriate countermeasures.
Note 2) Observe patient condition carefully and if abnormalities are identified, take appropriate countermeasures.

(4) List of adverse reaction frequencies and clinical laboratory test values

	Investigations until approval	Cumulative use performance study data	Totals
No. of study sites	130	341	429
No. of cases	747	1,268	2,015
No. of cases with adverse reaction	49	172	221
No. of adverse reactions	80	263	343
Adverse event frequency	6.56%	13.56%	10.97%

Types of adverse reactions	Studies until approval	Cumulative use performance study data	Totals
	No. of adverse reaction cases and onset rate (%) by type		
Skin/skin-related disorders	11 (1.47)	19 (1.50)	30 (1.49)
Eczema	1 (0.13)	1 (0.08)	2 (0.10)
Urticaria	3 (0.40)	-	3 (0.15)
Itching	5 (0.67)	4 (0.32)	9 (0.45)
Hair loss	-	6 (0.47)	6 (0.30)
Epilosis	1 (0.13)	-	1 (0.05)
Rash (skin rash)	4 (0.54)	8 (0.63)	12 (0.60)
Musculoskeletal disorders	1 (0.13)	1 (0.08)	2 (0.10)
Arthralgia	1 (0.13)	-	1 (0.05)
Muscle pain	-	1 (0.08)	1 (0.05)
Central/peripheral nervous system disorders	5 (0.67)	13 (1.03)	18 (0.89)
Stiff shoulders/neck	-	2 (0.16)	2 (0.10)
Vertigo	1 (0.13)	1 (0.08)	2 (0.10)
Limb tremors	1 (0.13)	-	1 (0.05)
Headache	1 (0.13)	4 (0.32)	5 (0.25)
Dull headache	-	2 (0.16)	2 (0.10)
Numbness of limbs	-	1 (0.08)	1 (0.05)
Numbness of fingers (sensation)	-	1 (0.08)	1 (0.05)
Numbness in limbs (sensation)	1 (0.13)	-	1 (0.05)
Dizziness	-	3 (0.24)	3 (0.15)
Lightheadedness	1 (0.13)	-	1 (0.05)
Sensory disorders	0 (0.00) -	1 (0.08)	1 (0.05)
Eye pain	-	1 (0.08)	1 (0.05)
Other special sensory disorders	0 (0.00)	1 (0.08)	1 (0.05)
Dysgeusia	-	1 (0.08)	1 (0.05)
Neurological disorders	1 (0.13)	7 (0.55)	8 (0.40)
Drowsiness	-	4 (0.32)	4 (0.20)
Insomnia (sensation)	-	2 (0.16)	2 (0.10)
Depressed state	1 (0.13)	2 (0.16)	3 (0.15)
Gastrointestinal disorders	22 (2.95)	48 (3.79)	70 (3.47)
Gastric ulcer	-	1 (0.08)	1 (0.05)
Nausea (nausea)	5 (0.67)	10 (0.79)	15 (0.74)
Vomiting	3 (0.40)	-	3 (0.15)
Diarrhea (loose stools)	4 (0.54)	5 (0.39)	9 (0.45)
Chapped lips	-	1 (0.08)	1 (0.05)
Stomatitis	2 (0.27)	3 (0.24)	5 (0.25)
Lip ulcer	1 (0.13)	-	1 (0.05)
Mouth dryness	1 (0.13)	-	1 (0.05)
Gingival swelling	-	1 (0.08)	1 (0.05)
Heavy feeling on stomach	1 (0.13)	1 (0.08)	2 (0.10)
Heartburn	2 (0.27)	1 (0.08)	3 (0.15)
Reduced appetite	6 (0.80)	10 (0.79)	16 (0.79)
Eating disorder	-	2 (0.16)	2 (0.10)
Tongue roughness	1 (0.13)	-	1 (0.05)
Stomach ache	-	2 (0.16)	2 (0.10)
Upset stomach	-	3 (0.24)	3 (0.15)
Upper abdominal pain	2 (0.27)	2 (0.16)	4 (0.20)
Lower abdominal pain	1 (0.13)	-	1 (0.05)
Right hypochondralgia	1 (0.13)	-	1 (0.05)
Ileoceal pain	1 (0.13)	-	1 (0.05)
Epigastric discomfort	1 (0.13)	2 (0.16)	3 (0.15)
Epigastricgia	1 (0.13)	2 (0.16)	3 (0.15)
Epigastric pressure	-	1 (0.08)	1 (0.05)
Constipation	-	2 (0.16)	2 (0.10)
Abdominal fullness	2 (0.27)	8 (0.63)	10 (0.50)
Borborygmus	-	1 (0.08)	1 (0.05)
Hepatobiliary disorders	4 (0.54)	83 (6.55)	87 (4.32)
Jaundice	-	7 (0.55)	7 (0.35)
Exacerbation of chronic Hepatitis	-	1 (0.08)	1 (0.05)
Liver abnormalities	-	1 (0.08)	1 (0.05)
Liver dysfunction	-	11 (0.87)	11 (0.55)
Exacerbation of liver function disorders	-	6 (0.47)	6 (0.30)
Liver dysfunctions (AST (GOT), ALT (GPT))	-	13 (1.03)	13 (0.65)
Liver damage	-	2 (0.16)	2 (0.10)
DNA polymerase elevation	-	4 (0.32)	4 (0.20)
AST (GOT) elevation			
ALT (GPT) elevation	4(0.54)	34 (2.68)	38 (1.89)
Elevated bilirubin	4(0.54)	36 (2.84)	40 (1.99)
Serum transaminase elevation	-	3 (0.24)	3 (0.15)
	-	5 (0.39)	5 (0.25)
Metabolic/nutritional disorders	1 (0.13)	3 (0.24)	4 (0.20)
LDH increase	-	1 (0.08)	1 (0.05)
Hypercholesterolemia	-	1 (0.08)	1 (0.05)
Urine sugar positive	1 (0.13)	-	1 (0.05)
Hypoalbuminemia	-	1 (0.08)	1 (0.05)
General cardiovascular disorders	2 (0.27)	1 (0.08)	3 (0.15)
Hypertension	1 (0.13)	1 (0.08)	2 (0.10)
Increased blood pressure	1 (0.13)	-	1 (0.05)
RBC disorders	0 (0.00)	1 (0.08)	1 (0.05)
Anemia	-	1 (0.08)	1 (0.05)
WBC/ Reticuloendothelial system disorders	4 (0.54)	2 (0.16)	6 (0.30)
Eosinophilia	3 (0.40)	-	3 (0.15)
Leukopenia	1 (0.13)	1 (0.08)	2 (0.10)
Leukemia	-	1 (0.08)	1 (0.05)
Platelet/coagulative disorders	0 (0.00) -	3 (0.24) 3 (0.24)	3 (0.15)
Thrombocytopenia	-	3 (0.24)	3 (0.15)
Female reproductive disorders	0 (0.00)	3 (0.24)	3 (0.15)
Menstrual irregularity	-	1 (0.08)	1 (0.05)
Menstrual extension	-	1 (0.08)	1 (0.05)
Amenorrhea	-	1 (0.08)	1 (0.05)
Generalized disorders	8 (1.07)	25 (1.97)	33 (1.64)
Chest pain	1 (0.13)	-	1 (0.05)
Fever	1 (0.13)	1 (0.08)	2 (0.10)
Fatigue	-	1 (0.08)	1 (0.05)
Malaise	6 (0.80)	1 (0.08)	7 (0.35)
General languor	-	20 (1.58)	20 (0.99)
Ascites	-	2 (0.16)	2 (0.10)
Edema	1 (0.13)	-	1 (0.05)

(At time of completion of re-examination)

(5) Underlying diseases, complications, severity, history of surgery, and frequency of other adverse reactions

No applicable materials.

(6) Warnings and test methods concerning drug allergies

Contraindications: Patients with a history of hypersensitivity to this germanium-based products Careful administration: Patients with a history of drug hypersensitivity

9. Use in the elderly

For older adults, please administer this product carefully while observing the patient's condition, such as starting administration from a lower dosage (e.g. 20mg/day). [Although this drug is mainly excreted via the kidneys, there is a risk of reaching unsafe high blood concentrations as renal function is often diminished in elderly patients.]

10. Use in pregnant, perinatal, or nursing women

(1) This product should only be administered to pregnant women or women who may become pregnant, if it is determined that the therapeutic benefit outweighs the risk. [Safety of use during pregnancy has not been established.] (2) Avoid administering this product to lactating women. If breastfeeding is necessary, stop use. [Migration into breast milk has been reported based on animal studies (rats)]

11. Use in infants and children

Product safety in infants and children has not yet been established (insufficient use experience).

12. Impact on clinical laboratory test results

No applicable materials.

13. Overdose

No applicable materials.

14. Warnings concerning indicated use

When dispensing this product: Instruct patients on how to remove this product from its PTP sheet packaging (there have been reports of accidental ingestion of PTP sheets and esophageal mucosal puncture wounds caused by sharp corners—such injuries can lead to serious complications such as mediastinitis or inflammation)

15. Other warnings

No applicable materials.

16. Other items

None.

IX. Nonclinical testing

1. Pharmacological testing

(1) Efficacy testing (refer to Section VI. Effects and efficacy)

(2) Secondary pharmacological tests

No applicable materials.

(3) Safety pharmacology tests [35)]

No significant adverse effects were observed as a result of examining the effects on the central nervous system, autonomic nervous system, smooth muscle, peripheral nervous system, respiratory/circulatory systems, digestive system, blood and urine in mice, rats, guinea pigs, rabbits and dogs.

(4) Other pharmacological tests

None.

2. Toxicity testing

(1) Single dose toxicity study[36,37)]

(LD_{50} mg/kg)

Animal species / Dosing method		Oral	IV	Intraabdominal	Subcutaneous*
Mice	♂	5600	>200	1250	>4000
	♀	5800	>200	1300	>4000
Rats	♂	7700	>200	1750	>4000
	♀	7050	>200	1670	>4000
Dogs	♂	>4000	—	—	—

*Maximally tolerated dose

(2) Repeated dose toxicity study

1) Rats

256–4,000mg/kg of propagermanium was orally administered to rats for 3 consecutive months. As a result, suppression of weight gain, increased water intake, loose stools/diarrhea, and other effects were observed. In addition, these changes all exhibited recovery or a recovery trend 1 month after termination of use. An ineffective dose in rats was estimated to be 256mg/kg[38)].

In another study, oral administration (83–750mg/kg) for 12 consecutive months resulted in loose stools/diarrhea, cecal enlargement, increased water intake, and similar effects. Each of these changes recovered 2 months after termination of use. In this study, an ineffective dose in rats was estimated to be 83mg/kg[39)].

2) Dogs

320–2,000mg/kg of propagermanium was orally administered to dogs for 3 consecutive months. As a result, loose stools/diarrhea, vomiting, salivation, mild weight loss, and increased water intake were observed. In addition, these changes all exhibited recovery or a recovery trend 1 month after termination of use. An ineffective dose in dogs was estimated to be less than 320mg/kg[40].

In another study, continuous oral administration (89–800mg/kg) for 12 consecutive months resulted in loose stools/diarrhea, vomiting, and other effects. Each of these changes recovered 2 months after termination of use. In this study, an ineffective dose in dogs was estimated to be less than 83mg/kg[39].

(3) Reproductive toxicity study

350, 700, and 1400mg/kg of propagermanium was given orally to rats before pregnancy and during early pregnancy, and 1000, 2000, and 4000mg/kg was given orally to rats in the organogenesis stage, and 75, 150, and 300mg/kg was given orally to rabbits in the organogenesis stage, and 750, 1500, and 3000mg/kg was given orally to perinatal and lactating rats. No effects on reproduction were observed as a result[42-45].

(4) Other specific toxicities

1) Antigenicity[46]

Antigenicity testing was conducted using the anaphylactic induction test in guinea pigs as well as polymerase chain reaction (PCA) and antibody tests, and precipitation reactions in agar gel using the Ouchterlony technique. No antigenicity was observed as a result.

2) Mutagenicity[47]

Mutagenicity testing was conducted using bacteria, chromosomal aberration tests using cultured cells, and micronucleus tests in mice. No mutagenicity was observed as a result.

3) Tumorigenicity[48,49]

Tumorigenicity tests were conducted after 78 weeks of oral administration of propagermanium to mice and 104 weeks of oral administration to rats, and no tumor formation was observed in any test animal.

X. Regulatory items

1. Regulatory classification

Preparation: Serocion capsules 10 for prescription use (Warning: may only be used in accordance with a physician prescription)

Active ingredient: propagermanium Not applicable

2. Shelf life or period of use

Three years from manufacture date (product must be used within the use period described on the product's external packaging).

3. Storage method/preservation conditions

Store at room temperature.

4. Warnings related to product handling

(1) Handling by pharmacies

None.

(2) Precautions at the time of dispensing of this product (essential points to consider for patients, etc.)

When dispensing this product: Instruct patients on how to remove this product from its PTP sheet packaging (there have been reports of accidental ingestion of PTP sheets and esophageal mucosal puncture wounds caused by sharp corners—such injuries can lead to serious complications such as mediastinitis or inflammation)

5. Product approval conditions

Not applicable.

6. Product packaging

100 capsules (PTP10 capsules×10)

7. Product packaging/container specifications

PTP: Polyvinyl chloride, aluminum foil pillow

Packaging: Polyethylene, individual aluminum foil wrapping

Box: Paper

8. Identical active ingredients/products with similar effects

Drugs with identical active ingredients: none

Drugs with similar effects: Interferon preparations (IFN-α, IFN-β, IFN-α-2a, IFN-α-2b)

9. International debut

Unknown.

10. Manufacturing/marketing authorization date and approval number

Manufacturing/marketing authorization date: July 1, 1994
Approval number: 20600AMZ01109000

11. NHI Drug Price List inclusion date

August 26, 1994.

12. Approval dates and details of additional effects or efficacies, dosages, or dosing methods

Not applicable.

13. Details and date(s) of publication of re-examination results

Date of publication of re-examination results: November 26, 2003
Details of re-examination result: No changes to "Effects and Efficacy" and "Dose and Dosing Method"

14. Re-examination period

July 1, 1994 – June 30, 2000

15. Information concerning drug products with restricted use periods

This product does not fall within the scope of "Drug products with restricted maximum use periods" as set forth in the partially amended Ministry of Health, Labor and Welfare (MHLW) Notification No. 97 (March 19, 2008) issued in conjunction with the Rules for Professionals in Charge of Healthcare Services and Dispensing Pharmacies and Pharmacists under Health Insurance Programs as well as the Standards for Healthcare Facilities and Professionals specified by the Minister of Health, Labor and Welfare (MHLW Notification No. 107 of March 19, 1999).

16. Product code numbers

Branded name	HOT No.	MHLW Standard Drug Price List Product Code	Medical receipt processing code
Serocion capsules 10	1084504	3919007M1021	610406385

17. Insurance coverage-related warnings

None.

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2. Other references cited

No applicable materials.

XII. Reference Materials

1. Sales conditions in major overseas markets

This product is not currently sold in the same formulation in overseas markets.

2. Supporting overseas clinical information

No applicable materials.

XIII. Notes

Other related materials

No applicable materials.