
An Integrative Interim Safety Overview of Two Open Label Studies with BM-MSCs

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Abstract

StromaForte is an allogeneic bone marrow-derived mesenchymal stromal cell (BM-MSC) investigational medicinal product under evaluation in two ongoing open-label clinical studies in The Bahamas. One study evaluates systemic administration in participants enrolled for cardiovascular-event prevention, and the second evaluates local and/or systemic administration in participants with musculoskeletal injury or degeneration.

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This manuscript summarizes an integrated interim safety analysis with a data cut-off of 10 March 2026. The safety population included all treated participants. Adverse events, serious adverse events, deaths, laboratory abnormalities reported as adverse events, vital signs, and supportive follow-up-time adjusted incidence rates were summarized descriptively.

The pooled safety population comprised 305 treated participants, contributing 329 patient-years of follow-up. Overall, 162 participants (53.1%) reported at least one adverse event, and 119 (39.0%) reported at least one treatment-related adverse event. Events were predominantly non-serious and were most often recorded under MedDRA System Organ Class (SOC) Investigations, largely reflecting protocol-defined clinically significant blood pressure or laboratory findings. Six participants (2.0%) experienced a serious adverse event; none were assessed as related to the study treatment. One death due to pancreatic carcinoma occurred 585 days after treatment and was assessed as unrelated. No adverse events leading to treatment discontinuation or dose modification were reported. No new safety signal, urgent safety measure, or safety-driven change to reference safety information was identified.

Based on available interim data, StromaForte demonstrated an acceptable and manageable safety profile in the studied populations and administration settings. Interpretation remains provisional because both studies are ongoing, follow-up is incomplete, laboratory follow-up is sparse, and repeated-dose experience remains limited.

Keywords: StromaForte, mesenchymal stromal cells, allogeneic cell therapy, safety, adverse events, phase I/IIa, pooled analysis.

Key Findings

In 305 treated participants contributing 329.1 patient-years of follow-up, administration of BM-MSCs was associated with a predominantly non-serious safety profile, and no treatment-related serious adverse events were reported through the 10 March 2026 data cut-off.

The most frequently reported adverse-event category was SOC Investigations, driven mainly by transient or clinically significant measurement and laboratory abnormalities recorded as adverse events, particularly systolic blood pressure increases and lipid-related findings.

No new safety signal, urgent safety measure, safety-driven discontinuation, or safety-driven change to reference safety information was identified.

The studies continue as planned with routine safety surveillance as per the study protocols.

Notations and Abbreviations

AE:	adverse event
AESI:	adverse event of special interest
BM:	bone marrow
CVD:	cardiovascular disease/cardiovascular-event prevention study
EDC:	electronic data capture
IMP:	investigational medicinal product
IV:	intravenous
MedDRA:	Medical Dictionary for Regulatory Activities
MSC:	mesenchymal stromal cell
MSD:	musculoskeletal disease/injury or degeneration study
PT:	preferred term
PY:	patient-years
SAE:	serious adverse event
SOC:	system organ class
AE:	adverse event

1 Introduction

Population aging is accompanied by a rising prevalence of chronic, non-communicable diseases that contribute substantially to morbidity, disability, health-care utilization, and loss of functional independence. Globally, the number and proportion of older adults continue to increase, with the World Health Organization estimating that the population aged ≥ 60 years will rise from approximately 1 billion in 2019 to 1.4 billion by 2030 and 2.1 billion by 2050 [1]. This demographic transition has intensified interest in biological processes that contribute to age-associated disease, particularly mechanisms that are shared across otherwise distinct clinical conditions. Among these, chronic low-grade inflammation, often termed “inflammaging,” has emerged as a central feature of aging biology and has been implicated in the development and progression of multiple age-related disorders [2, 3].

Inflammaging is characterized by persistent activation of innate and adaptive immune pathways, increased circulating inflammatory mediators, impaired resolution of inflammation, and altered tissue repair responses [2, 3]. Although aging itself contributes to this inflammatory milieu,

lifestyle, and metabolic factors, including physical inactivity, obesity, insulin resistance, and diets rich in saturated fats, may further amplify systemic inflammation. These processes are clinically relevant because chronic inflammation can promote endothelial dysfunction, vascular remodeling, extracellular matrix degradation, impaired tissue regeneration, and pain sensitization. Consequently, inflammation is increasingly recognized not only as a marker of disease burden but also as a potential therapeutic target across several chronic diseases of aging.

Cardiovascular disease (CVD) remains one of the leading causes of global morbidity and mortality and is strongly associated with aging. Atherosclerosis and related cardiovascular conditions are now understood as inflammatory as well as lipid-driven disorders. Activation of innate immune pathways, cytokine signaling, endothelial activation, and vascular inflammation contribute to plaque initiation, progression, and destabilization. The clinical relevance of inflammation in CVD has been supported by trials demonstrating that targeted anti-inflammatory therapy can reduce cardiovascular events independently of lipid lowering, including inhibition of the interleukin-1 β pathway in patients with prior myocardial infarction and elevated inflammatory risk [4]. These findings support the broader concept that modulation of inflammatory pathways may be relevant not only for the treatment of established CVD but also for strategies aimed at delaying or reducing disease progression in selected at-risk populations.

Musculoskeletal disorders are likewise highly prevalent with advancing age and represent a major cause of pain, disability, reduced mobility, and impaired quality of life. Although musculoskeletal disorders encompass a broad and heterogeneous group of conditions, several share biological features related to inflammation, tissue injury, altered repair, and degenerative remodeling. Osteoarthritis is a particularly relevant example. Traditionally viewed as a predominantly mechanical or “wear-and-tear” disease, osteoarthritis is now recognized as a whole-joint disorder involving cartilage, synovium, subchondral bone, menisci, ligaments, periarticular tissues, and inflammatory mediators [5, 6]. Synovial inflammation, macrophage activation, cytokine release, matrix-degrading enzymes, and altered chondrocyte responses have all been implicated in symptom generation and structural progression [5–7]. These observations have strengthened the rationale for interventions that target the inflammatory and reparative components of musculoskeletal disease, rather than focusing solely on structural degeneration.

Despite important differences in clinical presentation, CVD and musculoskeletal disorders may therefore share several pathobiological features,

including chronic low-grade inflammation, immune dysregulation, impaired endogenous repair, and adverse tissue remodeling. These overlapping mechanisms provide a rationale for investigating therapeutic approaches with broad immunomodulatory and regenerative properties. Mesenchymal stromal cells, also referred to as MSCs, are multipotent stromal cells that have been investigated across a wide range of inflammatory, degenerative, cardiovascular, and musculoskeletal indications. The International Society for Cellular Therapy has proposed minimal defining criteria for human MSCs, including plastic adherence in standard culture conditions, characteristic surface-marker expression, and capacity for trilineage differentiation *in vitro* [8]. However, the therapeutic rationale for MSCs in clinical development is now generally considered to extend beyond direct differentiation. MSCs may exert biological effects through paracrine signaling, secretion of extracellular vesicles, and soluble mediators, modulation of innate and adaptive immune responses, effects on macrophage polarization and other direct cell-to-cell interactions, and support of endogenous repair processes [9, 10].

These properties have made MSC-based investigational medicinal products of interest in conditions where inflammation, tissue injury, and impaired repair coexist. In cardiovascular contexts, MSCs have been explored for potential effects on inflammation, angiogenesis, fibrosis, and myocardial or vascular repair. In musculoskeletal conditions, MSCs have been investigated for their potential to modulate inflammatory joint environments, influence cartilage and subchondral bone biology, and support tissue repair responses. Although efficacy remains indication-specific and continues to require confirmation in adequately powered controlled trials, the breadth of MSC clinical investigation reflects a biologically plausible therapeutic platform relevant to several age-associated disorders.

As with all cell-based medicinal products, safety evaluation is a central component of clinical development. The safety profile of MSC therapy has been examined in systematic reviews and meta-analyses across clinical indications. Early pooled analyses concluded that MSC administration appeared generally safe, while emphasizing the need for larger controlled trials and rigorous adverse-event reporting [11]. More recent reviews have similarly reported no consistent signal for increased serious adverse events, mortality, infection, malignancy, or thrombotic complications, although transient fever and administration-related events have been observed in some settings [12]. Nevertheless, safety cannot be assumed to be uniform across products, tissue sources, manufacturing processes, routes of administration, dosing regimens, or patient populations. Product-specific and indication-specific safety data

therefore remain essential, particularly for allogeneic MSC products intended for use across chronic disease populations.

Here, we report an integrated interim safety analysis of StromaForte, a human allogeneic bone marrow-derived mesenchymal stromal cell investigational medicinal product. The analysis pools safety data from two ongoing open-label clinical studies evaluating the same investigational product in cardiovascular prevention and musculoskeletal populations. By integrating data across more than 300 exposed participants, this interim analysis provides a clinically meaningful opportunity to characterize adverse events, serious adverse events, and overall tolerability in two age-relevant therapeutic contexts. The objective of this paper is not to review the broader MSC efficacy literature, but to present a focused, publication-style summary of the emerging safety experience across two ongoing clinical studies.

2 Methods

2.1 Study Design and Data Sources

The two studies 2023-001-BHS and 2023-002-BHS are both open label studies with regulatory and ethical approval from the Ministry of Health, The Bahamas and the National Stem Cell Ethics Committee, The Bahamas. The studies began in 2023, and the data cut-off date was 10 March 2026. The two studies were registered on ClinicalTrials.gov as NCT06074783, a phase I/II study in participants with musculoskeletal injury and/or degeneration, and NCT06087848, a longitudinal phase I/IIa study evaluating safety and the prevention of cardiovascular events.

Both studies were designed primarily to evaluate the safety and tolerability of StromaForte following administration. The present analysis pooled available safety data from participants treated in either study at the time of interim data extraction. Because both trials are ongoing, open-label, and non-randomized, the analysis was descriptive in nature and focused on adverse events, serious adverse events, and clinically relevant safety observations following exposure to the investigational product. No formal hypothesis testing was planned for the pooled interim safety dataset.

2.2 Study Population

Eligible participants in the musculoskeletal study were male or female adults aged 18 years or older with musculoskeletal injury and/or degeneration. The study was designed to include participants with a broad range

of musculoskeletal conditions, including injuries or degenerative disorders affecting structures such as joints, muscles, tendons, ligaments, or bone. Participants could receive local treatment to the affected anatomical site when technically feasible, systemic intravenous treatment, or both, according to the clinical context and route feasibility.

The cardiovascular study enrolled adult male or female participants aged 25–85 years at inclusion for evaluation of the safety and potential preventive effects of intravenous StromaForte on cardiovascular events. Participants were followed longitudinally after treatment, with the study designed to capture cardiovascular outcomes over an extended follow-up period of 5 years. Cardiovascular risk stratification was planned to use established risk assessment approaches, including the atherosclerotic cardiovascular disease risk framework and complementary clinical questionnaires.

For the present integrated interim analysis, the safety population comprised all participants who received at least one dose of StromaForte in either of the two studies. Participants were analysed according to study indication and route of administration, where applicable.

2.3 Investigational Product

StromaForte is a human allogeneic bone marrow-derived *ex vivo* expanded mesenchymal stromal cell product. StromaForte was produced according to methods, which are under revision at the time of writing (Chaar *et al.* under review). On the day of injection, cryopreserved BM-MSCs were thawed in a 37°C water bath, washed to remove the cryoprotectant, and analyzed for viability and viable cell count. MSCs were resuspended in injection solution comprising equal volumes of 20% HSA and 0.9% sodium chloride and filled in syringes for administration within 2 hours of syringe preparation. MSCs were characterized by morphology and flow cytometry and were positive for CD73, CD90, and CD105, and negative for CD14, CD31, CD34, and CD45.

2.4 Treatment Administration

In the musculoskeletal study, eligible participants typically received between one–two local injections of StromaForte under ultrasound guidance into the injured and/or degenerated anatomical region. Dosing varied by route and clinical context, ranging from local administration of typically 50×10^6 cells to combined or multi-site dosing up to 200×10^6 cells per treatment occasion. Lower doses were on occasion administered for small joints, e.g. hands or fingers due to anatomical constraints. Participants could additionally receive

100×10^6 cells by slow intravenous push-infusion within the maximum allowed dose per treatment occasion. Intravenous administration alone was permitted when local injection at the site of injury or degeneration was not feasible. In both studies MSCs were not pooled.

In the cardiovascular study, participants received 100×10^6 StromaForte cells by slow intravenous push-infusion. Repeat doses could be administered at the discretion of the Principal Investigators.

2.5 Safety Assessments

Safety was the primary focus of both studies. Adverse events were collected after administration of StromaForte. Safety assessments included the occurrence, severity, seriousness, timing, duration, outcome, and relationship of adverse events to the investigational product and/or administration procedure, as assessed by the investigator, including clinically significant abnormal laboratory values reported as adverse events, and vital signs measured during safety surveillance post-treatment. Laboratory assessments post-treatment were voluntary for participants. Serious adverse events were defined according to standard regulatory criteria, including events resulting in death, life-threatening events, inpatient hospitalization or prolongation of hospitalization, persistent or clinically significant disability or incapacity, congenital anomaly or birth defect, or other medically important events.

In the musculoskeletal study, safety follow-up was scheduled at 1, 3, 6, and 12 months $\pm$ 10 days after treatment. The main safety endpoint was the number of adverse events and serious adverse events reported during follow-up.

In the cardiovascular study, safety and tolerability were assessed after treatment, with safety follow-up timepoints at 1 month, 6 months, 1 year, 3 years, and 5 years.

2.6 Integrated Interim Safety Analysis

Safety data from both ongoing studies were pooled to generate an integrated interim safety dataset. The pooled approach was considered appropriate because both studies evaluated the same investigational product, included systemic intravenous exposure to 100×10^6 allogeneic bone marrow-derived mesenchymal stromal cells, and used adverse event reporting based on the same criteria. Data were summarized overall and, where relevant, by study population, administration route, dose exposure, and timing of follow-up.

The number and proportion of participants experiencing at least one adverse event, serious adverse event, treatment-related adverse event, or treatment-related serious adverse event were summarized descriptively. Adverse events were tabulated by system organ class, preferred term, maximum severity, seriousness, and relationship to treatment. Events occurring after local administration, intravenous administration, or combined local and intravenous administration were described separately where attribution to route or procedure was clinically relevant.

No formal comparative statistical analyses were performed because both contributing studies were open-label and single-arm. Continuous variables were summarized using descriptive statistics, including number of observations, mean, standard deviation, median, and range, as appropriate. Categorical variables were summarized using counts and percentages, and missing data was not imputed. All analyses were performed on observed data available at the interim data cut-off.

The analysis was based on data extracted from live production EDC databases while both studies were ongoing. No database lock has been performed for this interim analysis, and data cleaning remained in progress at the time of report preparation. Additional information for serious adverse events was incorporated from SAE report forms stored in the trial master file. No other data sources were used for the integrated interim safety summary.

The safety population comprised all participants who received any amount of StromaForte by local injection and/or systemic infusion. Participants were summarized overall and, when relevant, by actual administration-route exposure group: local administration only, systemic administration only, or combined local plus systemic administration. The systemic-only group included participants from the CVD study and systemic-only participants from the MSD study. The local-only and combined local plus systemic groups were derived from the MSD study.

Exposure was summarized by number of treated participants, administration route, and number of administrations received through the cut-off date. Observation time for follow-up-adjusted summaries began at the date/time of first administration and continued until the earliest of study completion, early discontinuation, or data cut-off. Because treatment was intermittent rather than continuous, follow-up-time-adjusted incidence rates were interpreted as rates adjusted for observation time rather than as rates under continuous exposure.

Adverse events were coded using MedDRA version 28.0 and summarized by SOC and PT. For participants receiving multiple administrations, the AE

period was considered continuous from first administration through the end of follow-up. Event relationship to StromaForte was assessed by the investigator and grouped for analysis as related (possible, probable, or definite) or not related (none or unlikely). Serious adverse events were summarized regardless of causality.

Supportive analyses included follow-up-time-adjusted incidence rates for selected safety endpoints, expressed as events per 100 patient-years. Post-dose risk-window analyses (up to 7 days post administration of MSCs) were used to contextualize events plausibly associated with administration, including infusion- or injection-related reactions, vital-sign changes, pyrexia, chills, hypersensitivity-type events, and other acute observations. These analyses were descriptive. No hypothesis testing was performed. Because of staggered enrollment, differing study schedules, incomplete follow-up, and small subgroup sizes, comparisons across studies or administration-route groups should be interpreted cautiously.

3 Results

At the data cut-off, a total of 305 participants received at least one administration of StromaForte and were included in the pooled safety population. Of these, 175 participants were enrolled in the CVD study and 130 participants were enrolled in the MSD study. Overall, 237 participants (77.7%) remained ongoing, $n = 43$ (14.1%) completed participation in the study, and $n = 25$ (8.2%) had withdrawn early after treatment. Early withdrawal was due to loss to follow-up $n = 22$ (7.2%) and refusal of further follow-up ($n = 3$, 1.0%). No premature discontinuations were attributed to adverse events in the disposition categories summarized for the interim analysis. Participant baseline characteristics can be found in Table 1.

Follow-up completeness was limited at later protocol timepoints. In the CVD study, 55% of participants had reported data at the 1-year follow-up timepoint or later. In the MSD study, 66% of participants had reported data during the 6- to 12-month period after baseline. Participants who did not actively report early withdrawal or study completion were categorized as ongoing, and this category may include participants who are later classified as lost to follow-up.

The pooled dataset included 21 participants who received local administration only, $n = 96$ who received combined local plus systemic administration, and $n = 188$ who received systemic administration only. Overall, 272/305 participants (89.2%) received one administration, $n = 32$ (10.5%)

Table 1 Study population and exposure overview

Characteristic	Pooled	CVD Study	MSD Study
Participants, <i>n</i>	305	175	130
Age at inclusion, years (mean±SD)	55.4 ± 13.1	55.6 ± 13.4	55.1 ± 12.7
Height, cm, (mean±SD)	174.9 ± 9.9	175.7 ± 9.9	173.9 ± 9.9
Weight, kg, (mean±SD)	75.9 ± 15.7	76.0 ± 14.8	75.9 ± 17.0
BMI, kg/m ² , (mean±SD)	24.6 ± 3.8	24.5 ± 3.7	24.8 ± 3.9
Gender			
Male, <i>n</i> (%)	196 (64.3%)	107 (61.1%)	89 (68.5%)
Female, <i>n</i> (%)	109 (35.7%)	68 (38.9%)	41 (31.5%)
Ongoing at cut-off	237 (77.7%)	165 (94.3%)	72 (55.4%)
Completed study	43 (14.1%)	0	43 (33.1%)
Early withdrawal	25 (8.2%)	10 (5.7%)	15 (11.5%)
Any single administration	272 (89.2%)	154 (88.0%)	118 (90.8%)
Repeated administrations	33 (10.8%)	21 (12.0%)	12 (9.2%)
Total follow-up	329.1 patient-years	235.9 patient-years	93.2 patient-years

Data cut-off: 10 March 2026. CVD = study 2023-001-BHS-BHS; MSD = study 2023-002-BHS-BHS. Percentages are based on the treated safety population unless otherwise stated.

received two administrations, and one participant (0.3%) received four administrations, among participants receiving more than one administration, the median interval between doses was 251 days.

Overall, 162 participants (53.1%) experienced at least one AE, corresponding to 366 events. AEs were reported in 105/175 CVD participants (60.0%) and 57 of 130 MSD participants (43.8%). Related AEs were reported in 119 participants (39.0%), corresponding to 215 events. Related AEs occurred in 74 CVD participants (42.3%) and 45 MSD participants (34.6%). The overall profile was dominated by non-serious events and by findings recorded under Investigations, Vascular disorders, General disorders, and administration site conditions, and Nervous system disorders (Table 2).

The most frequently reported SOC was Investigations, reported in *n* = 106 (34.8%) and accounting for 169 events. This category was driven primarily by increased systolic blood pressure, reported in *n* = 69 (22.6%) and 75 events (Table 3). Other commonly reported Investigation PTs included increased high-density lipoprotein, increased blood cholesterol, decreased diastolic blood pressure, and increased diastolic blood pressure. These entries largely represent measurement or laboratory abnormalities classified as significant by the investigator and recorded as adverse events. They

Table 2 Overview of treatment-emergent adverse events

Category	CVD Study (<i>N</i> = 175)	MSD study (<i>N</i> = 130)	Pooled (<i>N</i> = 305)
Participants with any AE	105 (60.0%) [252 events]	57 (43.8%) [114 events]	162 (53.1%) [366 events]
Participants with any related AE	74 (42.3%) [149 events]	45 (34.6%) [66 events]	119 (39.0%) [215 events]
Participants with any SAE	2 (1.1%) [2 events]	4 (3.1%) [4 events]	6 (2.0%) [6 events]
Participants with any related SAE	0	0	0
AE leading to discontinuation	0	0	0
AE leading to dose modification	0	0	0
Deaths	1 (0.6%)	0	1 (0.3%)

Values are *n* (%) [events] where event counts were available. SAE = serious adverse event; AE = adverse event.

Table 3 Most frequent pooled AE system organ classes and selected preferred terms

SOC or PT	Pooled <i>n</i> (%) [events]	Interpretation
Any AE	162 (53.1%) [366]	Overall treated safety population.
Investigations	106 (34.8%) [169]	Primarily clinically significant measurement or laboratory abnormalities recorded as adverse events.
Blood pressure systolic increased	69 (22.6%) [75]	Most frequent PT; interpreted with vital-sign summaries.
Vascular disorders	34 (11.1%) [36]	Mainly hypertension and hypotension.
General disorders and administration site conditions	29 (9.5%) [40]	Most commonly fatigue.
Nervous system disorders	25 (8.2%) [31]	Dizziness, headache, and procedural headache were each reported in 2.0%.
Musculoskeletal and connective tissue disorders	13 (4.3%) [21]	Heterogeneous events; no consistent serious pattern.
Gastrointestinal disorders	10 (3.3%) [15]	Uncommon and heterogeneous.

SOC = system organ class; PT = preferred term. This table intentionally summarizes only selected high-level findings for manuscript readability.

should therefore be interpreted alongside the formal vital sign and laboratory summaries rather than as standalone clinical syndromes.

Over the whole follow-up period, Vascular disorders were reported in 34 participants (11.1%), primarily hypertension and hypotension. General

disorders and administration site conditions were reported in $n = 29$ (9.5%). Fatigue was one of the more commonly reported general disorders. Nervous system disorders were reported in $n = 25$ (8.2%), with dizziness, headache, and procedural headache each reported in 2.0% of participants (Table 3). Other SOC's were less frequent and included musculoskeletal and connective tissue disorders, gastrointestinal disorders, infections and infestations, respiratory disorders, psychiatric disorders, and surgical or medical procedures. At this interim stage, the pattern of non-serious events was consistent with transient administration-associated observations, expected intercurrent medical events, and protocol-defined measurement findings, rather than a clear pattern of serious or progressive toxicity.

Serious adverse events were infrequent, with $n = 6$ (2.0%) experiencing at least one SAE, with six total SAE events reported, of this $n = 2$ were from the CVD study (1.1%) and $n = 4$ from the MSD study (3.1%), with no SAE assessed as related to StromaForte. The SAE profile was clinically heterogeneous, with no apparent clustering by SOC or PT. The events included ovarian cancer, pancreatic carcinoma, Mallory–Weiss syndrome, road traffic accident, dementia, and finger amputation. The most frequently represented SOC was neoplasms benign, malignant, and unspecified, with two participants (0.7% pooled), but the two events were different malignancies and were each single-subject events.

One death was reported in the pooled safety dataset. The participant was enrolled in the CVD study, and the primary cause of death was pancreatic carcinoma, with the death occurring 585 days after treatment. The event was assessed by the investigator as not related to study treatment. No additional information was available in the source report regarding timing of diagnosis, preceding clinical course, or contributory factors beyond the cause and date of death. No AEs leading to treatment discontinuation and no AEs leading to dose modification were reported in either study or in the pooled population.

Formal adverse events of special interest (AESI) were not prespecified in the two study protocols and accordingly, no formal AESI analysis was performed. Nevertheless, selected potential clinical concerns were reviewed, including development of infection, malignancy, and thrombotic and embolic events. No pulmonary embolism, deep vein thrombosis, or serious thrombotic or embolic events were reported. One participant experienced superficial thrombophlebitis of the left arm, which was assessed by the investigator as mild and related to study treatment. Repeated and difficult venous access in the same arm for blood sampling and intravenous MSC infusion, as well as same-day air travel, were considered potential contributing factors. No additional thrombotic or embolic events were reported in either trial.

No events of sepsis or joint infection were reported. Infection-related events were predominantly mild and consistent with common infections expected in the general population. The integrated review did not identify a signal suggesting increased susceptibility to infections, severe infections, or opportunistic infections.

Three malignancies were reported, consisting of ovarian cancer, pancreatic carcinoma, and prostate cancer, occurring in one participant each. None were assessed by the investigators as related to study treatment.

Clinical laboratory interpretation was constrained by limited voluntary post-treatment laboratory follow-up, with only $n = 39$ (12.8%) undertaking safety laboratory testing at follow-up. Coverage was 34 of 175 participants (19.4%) in the CVD study and 5 of 130 participants (3.8%) in the MSD study. Within this limited dataset, clinically significant laboratory abnormalities reported as adverse events were predominantly lipid- and metabolic/endocrine-related. Increased blood cholesterol was reported in $n = 13$ (4.3%), increased blood testosterone in $n = 6$ (2.0%), increased low density lipoprotein in $n = 4$ (1.3%), and increased oestradiol in $n = 3$ (1.0%) (Table 5). Potential hepatic abnormalities were rare, with single-subject reports of an increase in alanine aminotransferase and aspartate aminotransferase. Overall, the available laboratory data did not show a consistent pattern of clinically significant laboratory toxicity, but the sparse follow-up substantially limits interpretability.

Vital signs included systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and body temperature assessed before treatment and at scheduled post-treatment timepoints. Pooled visit 2 and repeat-dose summary data did not show a consistent pattern of clinically meaningful central tendency change during the post-treatment observation period. Median systolic blood pressure was 125 mmHg pre-treatment and remained between 122 and 125 mmHg through minute 90 and at minute 240. Median diastolic blood pressure was 78 mmHg pre-treatment and remained generally between 72 and 78 mmHg across post-treatment timepoints. Median heart rate ranged from 61 to 69 beats/min compared with 68 beats/min pre-treatment; median respiratory rate remained 16 to 18 breaths/min; and median body temperature remained approximately 36.6 to 36.8°C.

A subgroup of 50 participants (16.4%) had post-treatment diastolic blood pressure increases of at least 5 mmHg and/or systolic blood pressure increases of at least 10 mmHg to greater than 140 mmHg at one or more timepoints. Fourteen of these participants also had pre-treatment readings greater than 140 mmHg. No participant had a severe blood pressure increase, as assessed

Table 4 Supportive follow-up-time adjusted incidence rates

Endpoint	Events	Events per 100 patient-years
Any AE	366	111.2
Treatment-related AE	215	65.3
Serious AE	6	1.8
Severe AE	9	2.7
AE leading to treatment discontinuation	0	0.0

Total follow-up was 329.1 patient-years. Rates adjust for observation time and should not be interpreted as continuous-exposure rates.

by investigators. Clinically significant day 0 vital-sign abnormalities were most often recorded as blood pressure systolic increased in 65 participants (21.3%). Other vital-sign abnormalities were less frequent. One participant had an acute body-temperature increase from 36.4°C pre-treatment to 38.6°C immediately after treatment and 39.0°C at 45 minutes; this event was assessed as possibly related. Isolated low temperature values were considered more likely to reflect measurement artefact than a meaningful safety signal.

Follow-up-time-adjusted incidence rates were used as supportive summaries because follow-up duration differed across studies and exposure groups (Table 4). In the overall treated population, the incidence rate for any AE was 111.2 events per 100 patient-years. The rate for treatment-related AEs was 65.3 events per 100 patient-years. Serious AEs and severe AEs remained uncommon, with rates of 1.8 and 2.7 events per 100 patient-years, respectively (Table 4). These rates support the descriptive conclusion that serious and severe outcomes were infrequent relative to overall observation time. Subgroup incidence-rate comparisons should be interpreted cautiously because they are affected by differences in follow-up duration, study procedures, small denominators, and recurrent event recording.

Post-dose risk-window analyses were used to contextualize acute tolerability. In the pooled route groups, any adverse event within 24 hours was reported in 6 of 21 local-only participants (28.6%), 93 of 188 systemic-only participants (49.5%), and 38 of 96 local plus systemic participants (39.6%). Any treatment-related adverse event within 24 hours was reported in $n = 6$ (28.6%), $n = 67$ (35.6%), and $n = 35$ (36.5%) participants, respectively. Similar proportions were observed within the 7-day window. These results suggest that a substantial proportion of reported events occurred in the immediate post-administration period, particularly vital-sign or Investigation-coded findings, but do not identify a new acute tolerability concern in the integrated population.

Table 5 Selected laboratory and vital-sign observations

Finding	Pooled Result	Comment
Post-treatment safety laboratory follow-up	39/305 participants (12.8%)	Interpretation limited by sparse laboratory follow-up.
Blood cholesterol increased	13 (4.3%) [14 events]	Most frequent laboratory abnormality reported as an adverse event.
Blood testosterone increased	6 (2.0%) [6 events]	Infrequent and primarily in systemically exposed participants.
Day 0 blood pressure systolic increased	65 (21.3%)	Most frequent clinically significant vital-sign abnormality.
Participants with post-treatment blood pressure increases meeting predefined thresholds	50 (16.4%)	No severe increases.
Population-level median vital signs	Generally stable	No sustained shift in pooled median vital-sign summaries.

Values are *n* (%) unless otherwise indicated. These findings should be interpreted as descriptive interim observations.

The integrated signal evaluation considered AE and SAE patterns, seriousness, relatedness, severity, administration route, number of administrations, follow-up-time-adjusted incidence rates, post-dose windows, laboratory findings, vital signs, deaths, and selected clinical concerns of thromboembolism, malignancy, and infection. No new safety signal was identified through the data cut-off. Ongoing monitoring remains appropriate for transient administration-associated vital-sign changes, particularly blood pressure changes around dosing; clinically significant laboratory abnormalities reported as adverse events, particularly lipid- and metabolic-related findings in participants with systemic exposure; and serious medical events arising during longer-term follow-up, including malignancy-related events, although no treatment-related pattern has been identified to date.

No urgent safety measure was required during the reporting period. No safety-driven suspension, termination, or material restriction of study treatment was considered warranted. No change to reference safety information was required, and no protocol amendment specifically attributable to an emerging safety concern was identified. Protocol amendments reflected in current protocol versions were described as non-safety-driven and related to

the removal of selected exploratory biomarker, inflammation, and healthy-longevity objectives and related procedures for logistical reasons and limited blood sampling. Existing protocol-defined safety monitoring procedures were considered adequate at this interim stage.

4 Discussion

This integrated interim analysis provides a cumulative overview for StromaForte across two ongoing open-label studies with 305 participants and more than 329 patient-years of follow-up. The overall safety profile observed through the cut-off date was characterized mainly by non-serious events, with serious events uncommon and none assessed as related to treatment. No deaths related to study treatment were reported, and no adverse events led to treatment discontinuation or dose modification. These findings support continued clinical investigation under routine safety surveillance.

A central feature of the observed adverse-event profile was the predominance of SOC Investigations-coded events. In the context of these protocols, Investigations included clinically significant vital-sign and laboratory abnormalities recorded as adverse events. The most common preferred term was an increase in systolic blood pressure, however median systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature were generally stable during the post-administration observation period. Thus, the Investigation signal appears to be driven largely by transient or isolated measurement abnormalities, rather than a persistent hemodynamic pattern at the population level. Blood pressure findings nevertheless deserve continued surveillance. A clinically relevant subgroup experienced post-treatment blood pressure increases. Although the integrated dataset does not demonstrate a persistent blood pressure signal, the immediacy of some observations around treatment supports continued careful monitoring before, during, and after administration, particularly in participants with pre-existing cardiovascular risk or elevated baseline blood pressure.

Laboratory findings were harder to interpret due to limited follow-up. Observed abnormalities were mainly lipid/metabolic- and endocrine-related, including increased blood cholesterol, increased low density lipoprotein, increased blood testosterone and increased oestradiol. Hepatic enzyme abnormalities were rare and scattered. These findings were non-specific, and lipid abnormalities in particular are commonly observed in adult populations. The available laboratory data did not suggest a consistent pattern of clinically significant toxicity; however, absence of evidence should not be interpreted

as evidence of absence because only 12.8% of the pooled population had post-treatment laboratory testing at follow-up or unscheduled visits. More complete laboratory follow-up would strengthen future safety assessments and help distinguish true post-treatment changes from background variability and ascertainment bias.

The serious adverse-event profile was heterogeneous and did not suggest clustering. Six participants experienced SAEs, none related to StromaForte. Events occurred across diverse clinical domains, including malignancy, gastrointestinal disease, injury, neuropsychiatric disease, and surgery/procedure-related outcomes. The single death due to pancreatic carcinoma occurred long after treatment and was assessed as unrelated. Continued long-term follow-up remains important, particularly because the CVD study includes multi-year observation and because malignancy-related events require careful contextual review in cell-therapy development. At this interim stage, however, no malignancy-related pattern was apparent.

Selected potential concerns commonly relevant to cell-therapy products were also reviewed at a high level. No pulmonary embolism, deep vein thrombosis, sepsis, or joint infection was reported. One superficial thrombophlebitis event occurred in the setting of repeated venous access and same-day air travel as a possible contributing factor. Infection-related events were predominantly mild, common infections, and the integrated review did not identify a signal suggesting increased susceptibility to infections, severe infections, or opportunistic infections. The reports of malignancy were clinically heterogeneous, and data did not demonstrate an increased malignancy risk nor identify direct proof of tumorigenicity. These findings are reassuring but remain limited by the ongoing and incomplete nature of follow-up.

The integrated analysis has several strengths. It pools safety data across two studies of the same investigational product, increasing the total exposure available for interim assessment. It uses harmonized safety definitions, MedDRA coding, investigator causality assessment, and both crude and follow-up-time-adjusted event summaries. It also incorporates SAE information from trial master file reports in addition to the EDC. Finally, the analysis explicitly acknowledges the limitations of live, unlocked clinical databases and presents the findings descriptively rather than as inferential comparisons.

The analysis also has important limitations. Both studies are open-label and single-arm, limiting causal inference. The planned registry-based control comparison for the CVD study had not been initiated and was not available for this safety summary. Follow-up duration and completeness differed across studies and participants as a result of staggered enrollment and distinct study

designs. Follow-up was incomplete, with only 55% of CVD participants having reported data at the 1-year timepoint or later and 66% of MSD participants having reported data during the 6- to 12-month period after baseline. Laboratory follow-up was sparse, and participants administered a repeat-dose was limited to 33 participants. The analysis was based on a live EDC database without database lock, so findings may change after continued data cleaning and reconciliation.

Because of these limitations, the results should be interpreted as provisional. The data are sufficient to support a top-level conclusion that no new safety signal had emerged and that the benefit-risk balance remained acceptable for continued clinical investigation. These results are not sufficient to establish comparative safety, to quantify rare-event risks precisely, or to make definitive statements about long-term safety. Future analyses should incorporate locked or more mature datasets, more complete follow-up, improved laboratory coverage, and appropriate comparator data when available.

5 Conclusions

Through the 10 March 2026 data cut-off, StromaForte demonstrated an acceptable and manageable interim safety profile across two ongoing open-label phase I/IIa studies. Among 305 treated participants, AEs were common but predominantly non-serious. Serious adverse events were infrequent, clinically heterogeneous, and assessed as unrelated to treatment. One death due to pancreatic carcinoma occurred 585 days after treatment and was assessed as unrelated. No AE led to treatment discontinuation or dose modification.

The principal safety observations requiring continued routine monitoring are transient administration-associated vital-sign changes, particularly blood pressure increases around dosing; clinically significant laboratory abnormalities reported as adverse events, especially lipid/metabolic and endocrine-related findings; and serious medical events during long-term follow-up. No new safety signal, urgent safety measure, or safety-driven change to reference safety information was identified. Continued safety surveillance and reassessment will continue, as will additional follow-up, efficacy data, laboratory data, and repeat-dose administration accrue.

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Conflicts of Interest

The authors include principal investigators, sub-investigators, a clinical study manager, and consultants affiliated with Cellcolabs Clinical Ltd., the sponsor of the studies.

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