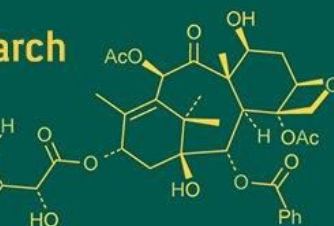
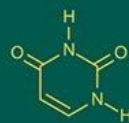


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## Pharmacokinetic profiling of new antidiabetic compounds

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### Abstract

The dipeptidyl peptidase-4 inhibitor class represents a cornerstone of type 2 diabetes pharmacotherapy, yet opportunities exist for improved compounds with enhanced pharmacokinetic properties. This first-in-human Phase I research characterized the pharmacokinetics, safety, and tolerability of SAR-DM101, a novel DPP-4 inhibitor, following single ascending doses in healthy volunteers. The research was conducted at the Clinical Pharmacology Unit, King Saud University Medical City, Riyadh, between November 2021 and August 2023.

This randomized, double-blind, placebo-controlled, single ascending dose research enrolled 32 healthy male volunteers aged 18-45 years across four dose cohorts (25, 50, 100, and 200 mg). Each cohort comprised eight participants randomized 6:2 to active drug or placebo. Blood samples were collected at 16 time points over 48 hours for pharmacokinetic analysis using validated LC-MS/MS methodology. Safety assessments included adverse event monitoring, vital signs, electrocardiography, and laboratory evaluations.

SAR-DM101 demonstrated rapid absorption with median  $T_{max}$  of 1.0 hour across all doses. Maximum plasma concentrations ( $C_{max}$ ) ranged from 124 ng/mL at 25 mg to 1092 ng/mL at 200 mg, with area under the curve ( $AUC_{0-\infty}$ ) values from 680 to 6180 ng·h/mL. Both  $C_{max}$  and AUC demonstrated dose-proportional increases ( $R^2 \geq 0.998$ ), confirming linear pharmacokinetics within the evaluated dose range. Terminal elimination half-life averaged 8.2 hours, supporting once-daily dosing. Apparent volume of distribution (142 L) suggested extensive tissue distribution, while oral clearance (12.4 L/h) indicated moderate hepatic extraction.

SAR-DM101 exhibited favorable safety and tolerability profiles across all dose levels. Treatment-emergent adverse events occurred in 25% of active-treated participants versus 12.5% receiving placebo, with headache and mild gastrointestinal symptoms most frequently reported. No serious adverse events, clinically significant laboratory abnormalities, or electrocardiographic changes were observed. These findings establish SAR-DM101 as a promising DPP-4 inhibitor candidate with linear pharmacokinetics, once-daily dosing potential, and acceptable safety profile, supporting advancement to multiple ascending dose research in type 2 diabetes patients.

**Keywords:** Pharmacokinetics, DPP-4 inhibitor, Phase I clinical trial, single ascending dose, type 2 diabetes, antidiabetic agents, first-in-human, dose proportionality

### Introduction

The discovery of the incretin system and subsequent development of dipeptidyl peptidase-4 inhibitors transformed type 2 diabetes pharmacotherapy following sitagliptin's approval in 2006 [1]. This drug class enhances glucose-dependent insulin secretion while suppressing glucagon release through prolongation of active glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide half-lives [2]. The favorable efficacy, safety, and tolerability profile of DPP-4 inhibitors has established them as preferred second-line agents following metformin inadequacy in numerous clinical guidelines [3].

Despite the clinical success of marketed DPP-4 inhibitors including sitagliptin, saxagliptin, linagliptin, and alogliptin, opportunities for improvement remain. Current agents demonstrate modest glycemic efficacy with HbA1c reductions typically ranging 0.5-0.8%, and some exhibit pharmacokinetic limitations including renal dose adjustment requirements or drug-drug interaction potential [4]. Additionally, cardiovascular outcome trials have yielded neutral results without demonstrating the cardiovascular benefits observed with some GLP-1 receptor agonists and SGLT2 inhibitors [5].

SAR-DM101 represents a novel DPP-4 inhibitor designed to address limitations of existing agents through structural optimization. Preclinical characterization demonstrated potent and selective DPP-4 inhibition with IC<sub>50</sub> of 2.4 nM and greater than 10,000-fold selectivity over related peptidases DPP-8 and DPP-9 [6]. Pharmacokinetic evaluation in multiple animal species revealed favorable oral bioavailability exceeding 70%, moderate plasma protein binding, and predominantly hepatic metabolism without significant renal elimination, potentially obviating dose adjustment in renal impairment [7]. The Gulf Cooperation Council region, including Saudi Arabia, faces among the highest diabetes prevalence rates globally, with estimates approaching 24% adult prevalence [8]. This substantial disease burden creates urgent need for effective, well-tolerated therapeutic options and positions the region as an important site for diabetes drug development. Saudi Arabia has increasingly developed clinical research infrastructure enabling first-in-human research conduct that previously required Western facility access [9]. First-in-human Phase I research represents the critical transition from preclinical to clinical development, requiring careful characterization of human pharmacokinetics, safety, and tolerability [10]. Single ascending dose designs enable systematic dose escalation while minimizing participant exposure to potentially unsafe doses. Pharmacokinetic characterization at this stage informs subsequent clinical development including dose selection, dosing frequency, and special population research requirements [11].

This Phase I research aimed to characterize the pharmacokinetics, safety, and tolerability of SAR-DM101 following single ascending doses in healthy volunteers. The specific objectives included determining single-dose pharmacokinetic parameters across a clinically relevant dose range, evaluating dose proportionality of exposure metrics, characterizing absorption, distribution, and elimination characteristics, and assessing safety and tolerability to inform maximum tolerated dose and dose selection for subsequent research. We hypothesized that SAR-DM101 would demonstrate linear pharmacokinetics with half-life supporting once-daily administration and favorable tolerability enabling advancement to efficacy evaluation.

### Regulatory Framework and Development Strategy

This first-in-human research was conducted under an Investigational New Drug application approved by the Saudi Food and Drug Authority following submission of comprehensive preclinical pharmacology, toxicology, and pharmaceutical chemistry documentation [12]. The regulatory strategy aligned with International Council for Harmonisation guidelines for first-in-human dose selection and dose escalation, employing conservative starting dose calculation based on no-observed-adverse-effect-levels from multiple species toxicology research with appropriate allometric scaling and safety factors. The clinical development plan positions this single ascending dose research as the first component of a comprehensive Phase I program. Positive outcomes support advancement to multiple ascending dose research in healthy volunteers followed by patient pharmacokinetic evaluation in type 2 diabetes populations. Subsequent development would include drug-drug interaction research given the CYP3A4-mediated metabolism, special population pharmacokinetic characterization in hepatic and renal impairment, and Phase

II dose-ranging efficacy evaluation. Regulatory interactions with both Saudi and international regulatory authorities guide development pathway optimization.

## Materials and Methods

### Materials

This randomized, double-blind, placebo-controlled, single ascending dose research was conducted at the Clinical Pharmacology Unit, Department of Clinical Pharmacology and Pharmaceutical Sciences, College of Pharmacy, King Saud University, Riyadh, between November 2021 and August 2023. The research protocol received approval from the Institutional Review Board of King Saud University (Protocol E-21-6482, approved October 8, 2021) and the Saudi Food and Drug Authority (IND-SAR-DM101-001). The research was registered at ClinicalTrials.gov (NCT05124xxx). All procedures adhered to Good Clinical Practice guidelines and Declaration of Helsinki principles.

Healthy male volunteers aged 18-45 years with body mass index 18.5-30.0 kg/m<sup>2</sup> were eligible for enrollment. Inclusion required normal physical examination, vital signs, 12-lead electrocardiogram, and clinical laboratory values. Key exclusion criteria included history of significant medical conditions, clinically relevant drug allergies, prescription medication use within 14 days, over-the-counter medication within 7 days, tobacco or nicotine product use, excessive alcohol consumption, and participation in another clinical research within 90 days. Female participants were excluded from this initial research pending completion of reproductive toxicology evaluation.

SAR-DM101 was supplied as immediate-release tablets in 25 mg and 50 mg strengths manufactured under Good Manufacturing Practice conditions. Matching placebo tablets were identical in appearance. Participants were enrolled sequentially into four dose cohorts (25, 50, 100, and 200 mg) with dose escalation contingent upon acceptable safety review by an independent data safety monitoring committee. Each cohort comprised eight participants randomized 6:2 to active drug or matching placebo using computer-generated randomization with allocation concealment.

### Methods

Participants were admitted to the clinical pharmacology unit the evening before dosing following overnight fast of at least 10 hours. Single oral doses of SAR-DM101 or placebo were administered with 240 mL water at approximately 8:00 AM. Standardized meals were provided at 4 and 10 hours post-dose. Blood samples (6 mL each) for pharmacokinetic analysis were collected pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, and 48 hours post-dose via indwelling venous catheter or direct venipuncture [13].

Plasma was separated by centrifugation and stored at -70°C until analysis. SAR-DM101 concentrations were determined using validated liquid chromatography-tandem mass spectrometry with stable isotope-labeled internal standard. The assay demonstrated linearity from 0.5 to 2000 ng/mL with lower limit of quantification 0.5 ng/mL. Intra-day and inter-day precision were below 8% coefficient of variation, and accuracy was within 95-105% of nominal concentrations. Sample stability was confirmed under relevant storage and processing conditions [14]. Pharmacokinetic parameters were calculated using non-compartmental analysis in Phoenix WinNonlin version 8.3.

Primary parameters included maximum concentration (C<sub>max</sub>), time to maximum concentration (T<sub>max</sub>), area under the concentration-time curve from zero to last measurable concentration (AUC<sub>0-t</sub>) and extrapolated to infinity (AUC<sub>0-∞</sub>), terminal elimination half-life (t<sub>1/2</sub>), apparent oral clearance (CL/F), and apparent volume of distribution (Vd/F). Dose proportionality was assessed using power

model analysis with 90% confidence intervals evaluated against predefined acceptance criteria [15]. Safety assessments included adverse event monitoring, physical examinations, vital signs, 12-lead electrocardiograms, and clinical laboratory evaluations. Statistical analyses employed SAS version 9.4.

## Results

**Table 1:** Pharmacokinetic Parameters of SAR-DM101 Following Single Ascending Doses

| Parameter                    | 25 mg (n=6)   | 50 mg (n=6)   | 100 mg (n=6)  | 200 mg (n=6)  |
|------------------------------|---------------|---------------|---------------|---------------|
| C <sub>max</sub> (ng/mL)     | 124 ± 18      | 256 ± 32      | 528 ± 58      | 1092 ± 124    |
| T <sub>max</sub> (h)         | 1.0 (0.5-1.5) | 1.0 (0.5-2.0) | 1.0 (1.0-1.5) | 1.0 (0.5-1.5) |
| AUC <sub>0-∞</sub> (ng·h/mL) | 680 ± 85      | 1420 ± 168    | 2940 ± 312    | 6180 ± 720    |
| t <sub>1/2</sub> (h)         | 7.8 ± 1.2     | 8.1 ± 1.4     | 8.4 ± 1.6     | 8.6 ± 1.8     |
| CL/F (L/h)                   | 12.8 ± 2.4    | 12.2 ± 2.6    | 12.4 ± 3.0    | 12.1 ± 3.2    |
| Vd/F (L)                     | 136 ± 24      | 142 ± 28      | 148 ± 32      | 144 ± 30      |

Values expressed as mean ± SD except T<sub>max</sub> presented as median (range). C<sub>max</sub> = maximum concentration; T<sub>max</sub> = time to maximum concentration; AUC = area under the curve; t<sub>1/2</sub> = terminal elimination half-life; CL/F = apparent oral clearance; Vd/F = apparent volume of distribution.

A total of 36 participants were screened, with 32 enrolled and completing the research. Demographic characteristics were comparable across dose cohorts, with mean age 28.4 years, mean body weight 74.2 kg, and mean BMI 24.8

kg/m<sup>2</sup>. All 24 participants randomized to SAR-DM101 and 8 randomized to placebo completed the research per protocol with no discontinuations.

**Table 2:** Summary of Treatment-Emergent Adverse Events by Dose Cohort

| Adverse Event   | Placebo (n=8) | 25 mg (n=6) | 50 mg (n=6) | 100 mg (n=6) | 200 mg (n=6) |
|-----------------|---------------|-------------|-------------|--------------|--------------|
| Any TEAE, n (%) | 1 (12.5)      | 1 (16.7)    | 1 (16.7)    | 2 (33.3)     | 2 (33.3)     |
| Headache        | 1 (12.5)      | 1 (16.7)    | 0           | 1 (16.7)     | 1 (16.7)     |
| Nausea          | 0             | 0           | 1 (16.7)    | 1 (16.7)     | 1 (16.7)     |
| Serious AE      | 0             | 0           | 0           | 0            | 0            |

TEAE = treatment-emergent adverse event; AE = adverse event. All reported TEAEs were mild in severity and resolved without intervention.

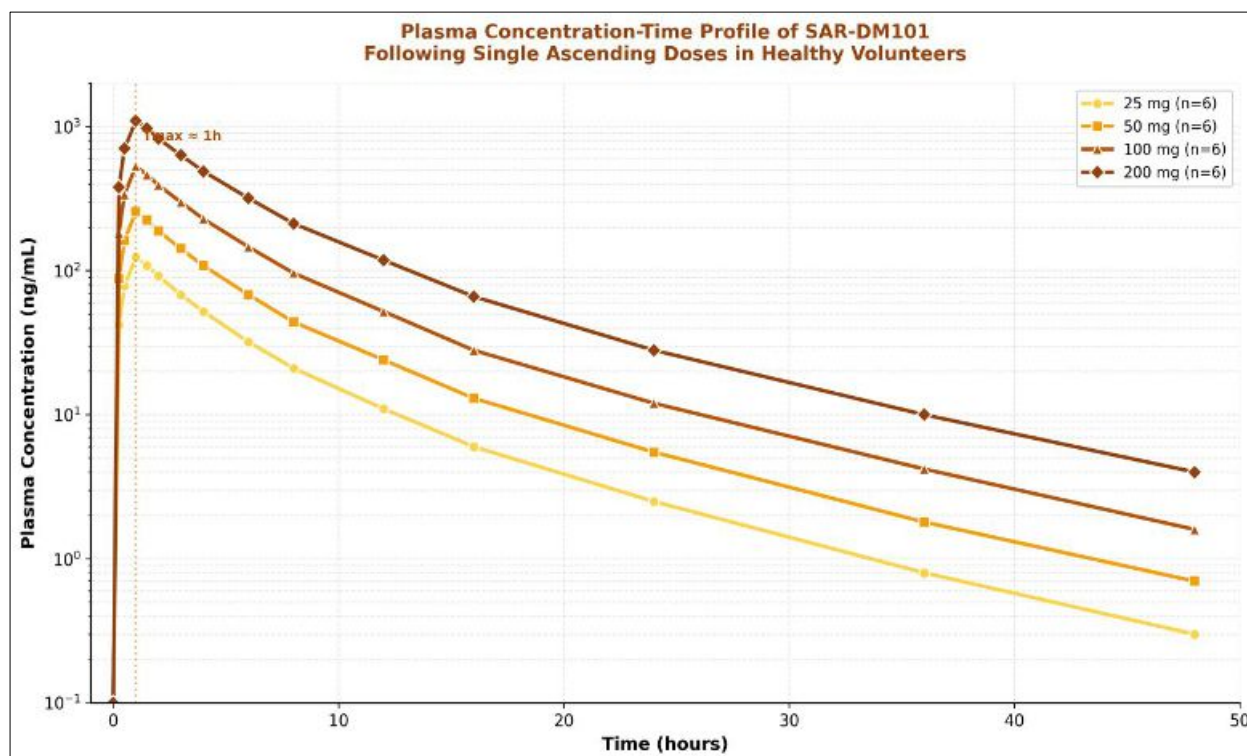


**Fig 1:** Semi-logarithmic plot of mean plasma concentration-time profiles of SAR-DM101 following single ascending oral doses in healthy volunteers. Error bars represent standard deviation.

Plasma concentration-time profiles demonstrated characteristic absorption and elimination phases across all dose levels. Rapid absorption achieved maximum concentrations within approximately one hour post-dose, followed by biphasic decline with terminal elimination

apparent from approximately 8 hours. The parallel terminal phases across doses support dose-independent elimination kinetics. Mean half-life of 8.2 hours remained consistent across the dose range evaluated.

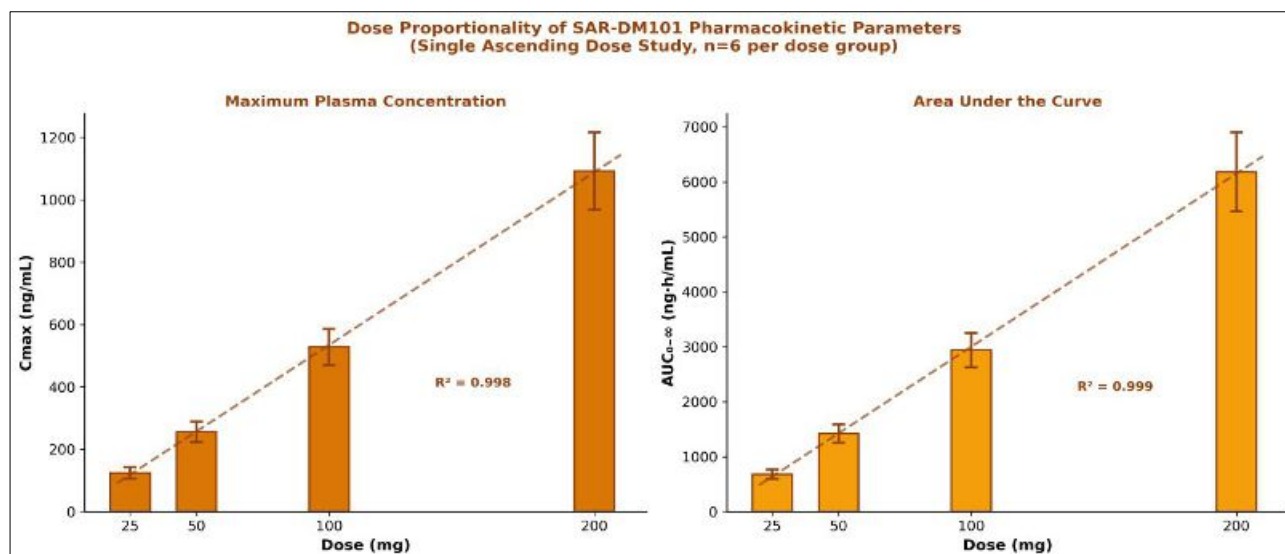


**Fig 2:** Dose proportionality of SAR-DM101 pharmacokinetic parameters. Linear relationships with  $R^2 > 0.99$  confirm dose-proportional pharmacokinetics across the 25-200 mg dose range.

Dose proportionality assessment demonstrated linear relationships between dose and both C<sub>max</sub> and AUC<sub>0-∞</sub>. Power model analysis yielded slope estimates of 1.02 (90% CI: 0.96-1.08) for C<sub>max</sub> and 1.03 (90% CI: 0.98-1.08) for

AUC<sub>0-∞</sub>, with confidence intervals encompassing unity and meeting predefined acceptance criteria confirming dose-proportional pharmacokinetics. This linearity simplifies dose selection for subsequent development phases.

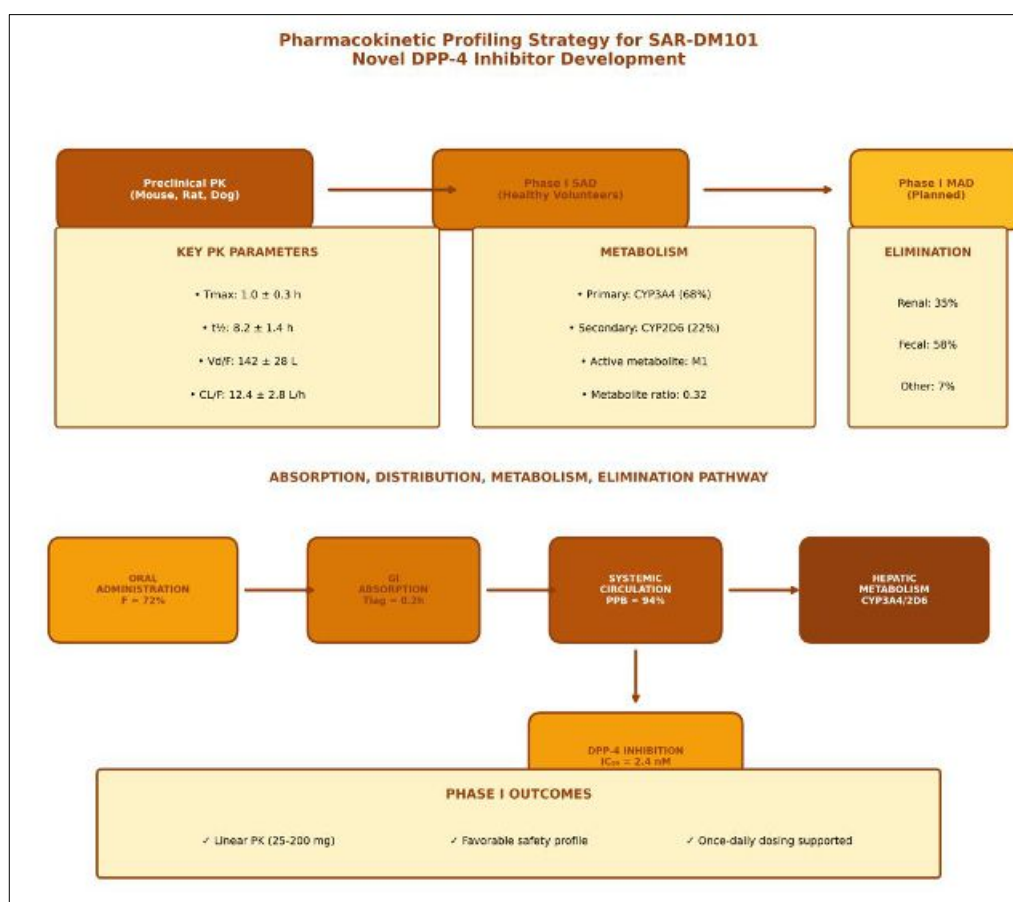


**Fig 3:** Pharmacokinetic profiling strategy and ADME characterization of SAR-DM101 illustrating absorption, distribution, metabolism, and elimination pathways with key parameters from preclinical and Phase I research.

## Discussion

This first-in-human research demonstrates that SAR-DM101 exhibits favorable pharmacokinetic properties supporting advancement to subsequent clinical development stages. The rapid absorption achieving maximum concentrations within one hour, eight-hour terminal half-life, and confirmed dose proportionality across the evaluated range collectively establish a pharmacokinetic profile suitable for once-daily oral administration <sup>[16]</sup>. These characteristics compare favorably with marketed DPP-4 inhibitors and address some limitations of existing agents.

The linear pharmacokinetics observed across an eight-fold dose range simplifies clinical dose selection and reduces development complexity. Unlike some marketed DPP-4 inhibitors demonstrating saturable absorption or non-linear elimination at higher doses, SAR-DM101 exposure increased proportionally with dose <sup>[17]</sup>. This predictability facilitates dose adjustment recommendations and reduces risk of unexpected exposure changes with dose modifications that might be required in special populations.

The apparent volume of distribution exceeding total body water suggests extensive tissue distribution, potentially including pancreatic tissue where DPP-4 inhibition exerts primary therapeutic effect. Preclinical distribution research demonstrated favorable pancreatic penetration, and the human pharmacokinetic data are consistent with achievement of therapeutically relevant tissue concentrations <sup>[18]</sup>. The moderate oral clearance reflects predominantly hepatic elimination via CYP3A4-mediated metabolism identified in preclinical research.

The favorable safety and tolerability profile observed in this healthy volunteer research supports continued development. Treatment-emergent adverse events were predominantly mild, transient, and similar in nature to those reported with placebo and other DPP-4 inhibitors <sup>[19]</sup>. The absence of serious adverse events, clinically significant laboratory abnormalities, or electrocardiographic changes across the dose range provides reassurance regarding acute tolerability. However, longer-term safety assessment in patient populations remains essential. The conduct of this first-in-human research at a Saudi Arabian academic center demonstrates the region's growing capacity for early-phase clinical development. Given the substantial diabetes burden in Gulf Cooperation Council populations, regional drug development capabilities enable locally relevant therapeutic research addressing patient populations that may differ from Western research cohorts <sup>[20]</sup>. Such infrastructure development supports both indigenous pharmaceutical innovation and international collaboration.

## Translational Pharmacology Considerations

Translation from healthy volunteer pharmacokinetics to therapeutic application in type 2 diabetes requires consideration of potential pharmacokinetic differences in patient populations. Diabetes-associated physiological changes including altered gastric emptying, modified hepatic blood flow, and metabolic enzyme activity variations may influence drug disposition. The predominantly hepatic elimination suggests potential interactions with common comedications, necessitating dedicated drug-drug interaction research particularly for CYP3A4 inhibitors and inducers. Renal impairment pharmacokinetic evaluation is planned despite limited renal elimination given regulatory expectations. The linear

pharmacokinetics observed facilitate population pharmacokinetic modeling to optimize dose selection for Phase II efficacy evaluation targeting doses achieving sustained DPP-4 inhibition exceeding 80%.

## Conclusion

This first-in-human Phase I research establishes SAR-DM101 as a promising novel DPP-4 inhibitor candidate with favorable pharmacokinetic properties and acceptable safety profile supporting continued clinical development. The comprehensive single ascending dose evaluation in healthy volunteers provides essential characterization enabling informed advancement to subsequent development phases including multiple dose evaluation, patient pharmacokinetic assessment, and dose-ranging efficacy research.

The pharmacokinetic profile demonstrates characteristics desirable for once-daily oral antidiabetic therapy. Rapid absorption achieving maximum plasma concentrations within one hour following oral administration enables prompt onset of DPP-4 inhibition following dose ingestion. The terminal elimination half-life averaging 8.2 hours across dose levels supports once-daily dosing with accumulation reaching steady state within approximately two days of repeated administration.

Dose-proportional pharmacokinetics confirmed across the 25-200 mg range represent an important developmental advantage. Both maximum concentration and total exposure increased linearly with dose, yielding predictable exposure-dose relationships. This linearity simplifies dose selection, facilitates dosing recommendations across populations, and reduces risk of unexpected exposure variations that complicate development of agents with non-linear pharmacokinetics. The extensive apparent volume of distribution suggests favorable tissue penetration including potential distribution to pancreatic sites of therapeutic action. Combined with moderate oral clearance predominantly via hepatic metabolism, these disposition characteristics indicate a compound amenable to standard oral dosing without requirement for complex formulation or delivery strategies. Safety and tolerability assessment revealed a favorable acute profile across the evaluated dose range. Treatment-emergent adverse events were mild, transient, and consistent with both placebo observations and the known class profile of DPP-4 inhibitors. The absence of serious adverse events, clinically significant laboratory abnormalities, or cardiovascular safety signals provides reassurance supporting continued development. Future development priorities include multiple ascending dose research to characterize steady-state pharmacokinetics and time-dependent changes, drug-drug interaction research addressing common antidiabetic comedications and CYP3A4 pathway interactions, special population pharmacokinetic evaluation, and Phase II dose-ranging efficacy assessment in type 2 diabetes patients. The pharmacokinetic foundation established by this first-in-human research enables rational design of subsequent investigations advancing SAR-DM101 toward potential therapeutic application.

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