Study to Evaluate the Safety and Efficacy of Oral Insulin Formulation in Type 2 Diabetes Mellitus Subjects

NCT06473662

06/19/2024

STUDY OBJECTIVES

Primary Objective

To evaluate the safe and effective dose of USVCAP (75 IU, or 150 IU, or 300 IU) after twice daily treatment with selected fixed dose (75 IU, or 150 IU, or 300 IU) of USVCAP for 12 weeks

Secondary Objective

To assess the immunogenicity of the investigational product

INVESTIGATIONAL PLAN

Overall Study Design and Plan-Description

Overview of Study Design

This was a phase IIb, open-label, randomized, comparative study to evaluate the safety and efficacy of USVCAP formulation in T2DM subjects uncontrolled with metformin hydrochloride treatment.

Total of 153 subjects who met the eligibility criteria were randomized in a ratio of 1:1:1 to any one of the following 3 treatment groups:

- Group A: USVCAP 75 IU, BD for 12 weeks
- Group B: USVCAP 150 IU, BD for 12 weeks
- Group C: USVCAP 300 IU, BD for 12 weeks

Each subject had following study periods and visits:

- Screening period (Visit 1): It lasted for up to 21 days after signing the informed consent form (ICF)
- Treatment period (Visit 2 to Visit 7): Eligible subjects were randomly assigned to any one of the above treatment groups at Visit 2 by randomization process through an interactive web response system (IWRS). Each subject from all 3 treatment groups received *assigned fixed dose of USVCAP (i.e. IP) as per allocated treatment groups for 12 weeks.

*Assigned fixed dose in the study is defined as: Fixed dose of USVCAP (i.e. IP) administered to subject twice daily for 12 weeks based on the treatment group (Group A, Group B, or Group C) allocated at randomization visit.

- Upon randomization:
    - Subjects allocated to Group A were prescribed with the assigned fixed dose of USVCAP (75 IU BD) from next day of randomization (Day 1) for 12 weeks
    - Subjects allocated to Group B and Group C, underwent a run-in period of 1 week with each previous lower dose/s, prior to initiation of assigned fixed dose of USVCAP. They additionally visited the study site for a step-wise increase of dose/s at each run-in period/s. These visits were called dose escalation (DE) visits (Visit DE 1 and Visit DE 2) in the trial. The dose increase were done once for Group B and twice for Group C subjects as depicted in Table 2 and Table 3. Upon completion of the run-in period/s, the

subjects received the assigned fixed dose of USVCAP further for 12 weeks (Table 2). Therefore, the overall duration of treatment with USVCAP for subjects in Groups B and C was 13 and 14 weeks, respectively
    - End-of-treatment: The end-of-treatment (EOT) for each randomized subject was defined as Day when 12-weeks of twice daily administration of assigned fixed dose of IP was completed by a subject (Table 2 and Table 3)
    - Visit 7 was the EOT visit: It was conducted on next day after the subject had completed twice daily administration of assigned fixed dose of IP for 12 weeks (Table 2)
- Post-treatment safety follow-up period: It was of 4-weeks duration after the subject had completed administration of the last dose of assigned fixed dose of IP. Visit 8 was the end-of-study (EOS) Visit in the study.

The Investigator followed the schedule of study assessments and procedures provided in Table 2. A window period of +2 days was allowed at every visit from Visit 3 to Visit 8 and at Visit DE 1 and Visit DE 2.

Pre-study oral anti-diabetic treatment (i.e. monotherapy with metformin hydrochloride) was continued at same dose and regimen from screening up to EOT period. A subject diary was provided to the subjects for recording the IP dosage, capillary glucose measurements, AEs, details on hypoglycaemic episodes, and any change in concomitant medications, as applicable.

The following Standard of Care was provided to each subject throughout the treatment period:

1. Step-wise dose escalation in subjects assigned to receive higher doses of USVCAP (i.e. subjects assigned to received fixed dose of 150 IU and 300 IU, BD)
2. Pre-study oral anti-diabetic monotherapy (i.e. metformin hydrochloride) continued at same dose and regimen
3. Capillary glucose measurements
4. Consumption and maintenance of healthy diet and lifestyle regimen
5. Treatment for complications related to insulin therapy (e.g. hypoglycaemia, hypokalaemia, etc.) or any other complications as per Investigator's practice and standard treatment guidelines

The Schedule of Study Procedures and Assessments is given in Table 3.

Table 1 Duration of Run in period(s) and treatment for doses of IP per each Allocated Treatment Group

Treatment Group	Assigned fixed dose of USVCAP	Treatment duration with assigned fixed dose of USVCAP	Run-in period/s with lower dose/s of USVCAP	Overall total duration of treatment with USVCAP
Group A	75 IU BD	12 weeks	Not applicable	12 weeks
Group B	150 IU BD	12 weeks	75 IU dose, BD for 1 week	13 weeks
Group C	300 IU BD	12 weeks	Overall 2 weeks of run-in period 75 IU BD for 1 week 150 IU BD for 1 week	14 weeks

Table 2 Schedule of Study Procedures and Assessments: As per allocated treatment groups

Study period	**Screening period**	**Start of Treatment period**	**Run-in period**		**Treatment period**					**Post- treatment Follow-up**
Visit Title	**Screening**	**Randomization/ Enrolment visit**	**Dose Escalation Visit(s)** *(only for subjects in Group B and Group C)*		**Treatment visits for assigned dose group**				**EOT[a]**	**EOS[b]**
Visit #	**1**	**2**	**DE 1[c]**	**DE 2[d]**	**3**	**4**	**5**	**6**	**7**	**8**
Group A (assigned dose 75 IU)	**Days -21 to 0**	**Day 0**	**N/A**	**N/A**	**8**	**15**	**30**	**60**	**85**	**114**
Group B (assigned dose 150 IU)	**Days -21 to 0**	**Day 0**	**8**	**N/A**	**15**	**22**	**37**	**67**	**92**	**121**
Group C (assigned dose 300 IU)	**Days -21 to 0**	**Day 0**	**8**	**15**	**22**	**29**	**44**	**74**	**99**	**128**
Window period			**+ 2 days (applicable for both DE1 and DE 2 visits)**		**+ 2 days (applicable at each visit)**					**+ 2 days**
Informed Consent	X									
Inclusion/Exclusion Criteria	X	X[e]								
Medical and Surgical history (including relevant details related to T2DM)	X	X[f]								
Prior medication (including anti-diabetic therapy)	X	X[g]								
Demographics with height (cm)	X									
Physical examination	X	X			X	X	X	X	X	X
Body weight (kg)	X	X	X	X	X	X	X	X	X	X
Waist circumference (cm)	X	X			X	X	X	X	X	X
Body mass index (kg/m^2)	X	X			X	X	X	X	X	X
Vital signs[h]	X	X	X	X	X	X	X	X	X	X
Randomization		X								
Dispensing of IP		X[i]	X[j]	X[k]	X	X	X	X		
(as per allocated treatment group)										
Accountability & compliance check of IP		X	X	X	X	X	X	X	X	

Study period	**Screening period**	**Start of Treatment period**	**Run-in period**		**Treatment period**					**Post- treatment Follow-up**
Visit Title	**Screening**	**Randomization/ Enrolment visit**	**Dose Escalation Visit(s)** *(only for subjects in Group B and Group C)*		**Treatment visits for assigned dose group**				**EOT[a]**	**EOS[b]**
Visit #	**1**	**2**	**DE 1[c]**	**DE 2[d]**	**3**	**4**	**5**	**6**	**7**	**8**
Group A (assigned dose 75 IU)	**Days -21 to 0**	**Day 0**	**N/A**	**N/A**	**8**	**15**	**30**	**60**	**85**	**114**
Group B (assigned dose 150 IU)	**Days -21 to 0**	**Day 0**	**8**	**N/A**	**15**	**22**	**37**	**67**	**92**	**121**
Group C (assigned dose 300 IU)	**Days -21 to 0**	**Day 0**	**8**	**15**	**22**	**29**	**44**	**74**	**99**	**128**
Window period			**+ 2 days (applicable for both DE1 and DE 2 visits)**		**+ 2 days (applicable at each visit)**					**+ 2 days**
Capillary glucose measurements		During the run-in period for Group B and C, at mid-week up to 1 day prior to withdrawal of blood samples for FPG and 2-hour PPG tests.			Weekly basis (i.e. once every week)					
		Every week for 4 time-points in a day (i.e. at fasting: 8-10 hours of overnight fasting, and 2-hours post-breakfast, post lunch and dinner). All 4 time-points were measured on the same day								
Dispensing of subject diary		X	X	X	X	X	X	X		
Subject diary review and collection			X	X	X	X	X	X	X	
Recording of AEs	X	X	X	X	X	X	X	X	X	X
Recording of concomitant medications	X	X	X	X	X	X	X	X	X	X
Laboratory investigations										
FPG[n]	X		X[l]	X	X	X		X	X	
2-hour PPG[m]	X		X[l]	X[l]	X	X		X	X	
HbA1c	X								X	
Haematology – RBC	X									
Hb, platelets, WBC with differential blood count										
Lipid profile: Total cholesterol, HDL, LDL, VLDL, and triglycerides after at least 12 hours of fasting	X								X	
Liver function tests- ALT, AST, ALP & Total bilirubin	X								X	

Study period	**Screening period**	**Start of Treatment period**	**Run-in period**		**Treatment period**					**Post- treatment Follow-up**
Visit Title	**Screening**	**Randomization/ Enrolment visit**	**Dose Escalation Visit(s)** *(only for subjects in Group B and Group C)*		**Treatment visits for assigned dose group**				**EOT[a]**	**EOS[b]**
Visit #	**1**	**2**	**DE 1[c]**	**DE 2[d]**	**3**	**4**	**5**	**6**	**7**	**8**
Group A (assigned dose 75 IU)	**Days -21 to 0**	**Day 0**	**N/A**	**N/A**	**8**	**15**	**30**	**60**	**85**	**114**
Group B (assigned dose 150 IU)	**Days -21 to 0**	**Day 0**	**8**	**N/A**	**15**	**22**	**37**	**67**	**92**	**121**
Group C (assigned dose 300 IU)	**Days -21 to 0**	**Day 0**	**8**	**15**	**22**	**29**	**44**	**74**	**99**	**128**
Window period			**+ 2 days (applicable for both DE1 and DE 2 visits)**		**+ 2 days (applicable at each visit)**					**+ 2 days**
Renal function tests- Serum creatinine, BUN, eGFR, sodium, potassium, chloride	X								X	
Total protein	X								X	
A/G ratio	X								X	
Calcium, Phosphorus, Vitamin D, PTH	X								X	
Urine Pregnancy test (females of childbearing potential or ≤ 1 year postmenopausal prior to enrolment	X								X	X
Insulin antibody test	X								X	X
Urine analysis: Routine	X									
Serology tests for HIV, HBV, HCV	X									
12-Lead ECG	X								X	

AE: adverse event; **A/G ratio:** albumin to globulin ratio **ALP: a**lkaline phosphatase; **ALT**: alanine aminotransferase; **AST**: aspartate aminotransferase; **BP**: blood pressure; **BUN:** blood urea, nitrogen; **DE:** dose escalation; **ECG**: electrocardiogram; **eGFR:** estimated glomerular filtration rate; **EOT:** end of treatment; **FPG:** fasting plasma glucose; **HIV:** human immunodeficiency virus; **HBV:** hepatitis B virus; **HCV:** hepatitis C virus; **EOS:** end-of-study; **EOT**: end-of-treatment, **IP:** investigational product; **PPG:** postprandial plasma glucose; **PR:** pulse rate; **PTH:** parathyroid hormone **RR:** respiratory rate; **SAE:** serious adverse event; **T2DM:** type 2 diabetes mellitus

a: Visit 7 was the EOT visit. was conducted on the next day after the subject had completed twice daily administration of fixed assigned dose of IP for 12-weeks.
b: Visit 8 was the EOS visit. It occurred at completion of 4-week post-treatment follow-up period
c: It was applicable for Group B and Group C subjects d: It was applicable for Group C subjects only
e: Review of eligibility criteria prior to randomization
f: Review of MH and surgical details prior to randomization

g: Review of any change in prior dose of metformin hydrochloride (non-IP) or prior medications
h: Systolic and diastolic BP (mmHg), PR (beats/min), RR (breaths/min) were measured after the subject was in supine position for 5 minutes and body temperature (°F). i: For all groups USVCAP capsules were dispensed considering 75 IU dose, BD
j: For Group B and C subjects USVCAP capsules were dispensed considering 150 IU dose, BD dose after reviewing the FPG and 2-hour PPG results. k For Group C subjects USVCAP capsules were dispensed considering 300 IU dose, BD after reviewing the FPG and 2-hour PPG results
l: It was evaluated prior to dispensing doses at DE 1 and DE 2 visits m: Blood samples were collected 2-hours after meal
n: Additional FPG measurements can be taken if capillary glucose measurements are abnormal, as defined in the protocol

Description of Study Visits

Visit 1/Up to 21 days

The screening procedure and assessments started only after signing of the ICFs. A subject was enrolled within 21 days of performing procedures/investigations for screening. Upon obtaining the informed consent, the subjects were allocated a unique subject identification (Subject ID) number and were screened to confirm the eligibility for participating in this study. Subjects who fulfilled the eligibility criteria were randomized in the study, while subjects who did not fulfilled the eligibility criteria were termed as 'screen failures'

The screening procedures and assessments were conducted as described below:

- Informed consent procedure: Written and signed informed consent were obtained from all subjects prior to conduct of any study procedures.
- Inclusion and exclusion criteria were checked
- Recording of medical/surgical history including relevant details related to T2DM
    - Date of diagnosis of T2DM. If complete date was not available, the year and month was recorded. If month was not available, at least year of diagnosis was recorded
    - History of alcohol dependency/drug abuse and/or was a current alcohol/drug abuse dependent
    - History of smoking or tobacco chewing and/or was a current smoker/tobacco user
- Recording of prior medication history (including current anti-diabetic medication, previous anti-diabetic therapy within 3 months prior to enrolment)
- Collection of demographic information, including height (cm)
- Recording of findings from physical examination
    - Recording of body weight (kg), waist circumference (cm) and body mass index (BMI) (kg/m^2)
    - Recording of vital signs: Systolic BP (SBP) and diastolic BP (DBP) (mm/Hg), pulse rate (PR) [beats/min], respiratory rate (RR) [breaths/min] in supine position after 5 minutes of rest and body temperature (degree Fahrenheit [°F])
- Laboratory investigations:
    - Blood samples were withdrawn from the subject to conduct the following laboratory investigations at a central laboratory:
        - Fasting Plasma Glucose
        - Postprandial plasma glucose (2-hours after meal)
        - HbA1c
        - Haematology: Red blood cells (RBCs) count, haemoglobin (Hb), platelet count, white blood cells (WBCs) count including differential count
        - Lipid profile: Total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), very low density lipoprotein (VLDL), and triglycerides after 12 hours of fasting
        - Liver function tests: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), Alkaline phosphatase (ALP), and total bilirubin

        - Renal function tests: Serum creatinine, blood urea nitrogen (BUN), sodium, potassium, chloride, and estimated glomerular filtration rate (eGFR)
        - Total protein & Albumin to globulin ratio (A/G ratio)
        - Calcium, phosphorus, vitamin D, Parathyroid hormone (PTH)
        - Serology tests: human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV) tests
        - Insulin Antibody test- Anti insulin antibody test
    - Urine samples were collected for:
        - Urine pregnancy test (UPT): Only for female subject of childbearing potential or who are ≤ 1 year postmenopausal prior to enrolment
        - Urinalysis: routine examination
- Recording of 12 Lead electrocardiogram recording (ECG)
- Recording of AE/ serious adverse events (SAEs), if any
- Recording of concomitant medications, if any

Visit 2 (Baseline Visit/ Randomization/ Enrolment Visit)

The following procedures and assessments were performed at this visit:

- Review of inclusion and exclusion criteria obtained during screening procedures and assessments
- Review of medical and surgical history recorded at Visit 1
- The following details were recorded at this visit:
    - Findings of physical examination
    - Body weight (kg) and waist circumference (cm) and body mass index (BMI) (kg/m^2)
    - Vital signs: SBP and DBP (mmHg), PR (beats/min), RR (breaths/min) after 5 minutes of rest and body temperature (degree Fahrenheit [°F]) in supine position
    - AE/SAE, if any
    - Prior and concomitant medications, if any
- Training to perform capillary glucose measurements. (Appendix 16.1.13 for detail).
- Subject randomization using IWRS (prior to dispensing of 1st dose of IP)
- Dispensing of IP: The subjects were dispensed IP doses during the treatment period (including the run-in period) as per the dose required per allocated treatment groups (Group A, Group B or Group C).
    - At this visit only: All subjects randomised to Group A, B, and C were dispensed USVCAP capsules of dose strength 75 IU
    - Subjects randomised to Group A were prescribed 1 capsule of USVCAP (i.e. assigned fixed dose 75 IU, BD for 12 weeks) from next day (i.e. Day 1) after randomisation. They were instructed to visit the study site for their next scheduled visit (Visit 3 [Day 8 [+2 days])

- Subjects randomised to Groups B and C were prescribed 1 capsule of USVCAP (i.e. lower dose [75 IU BD] based on the assigned fixed doses - 150 IU, BD for 12 weeks [Group B] and 300 IU, BD for 12 weeks [Group C]) from next day after randomisation (i.e. on Day 1). They were instructed to visit the study site for their next scheduled visit (Visit DE 1/Day 8 [+2 days])
- Subjects randomised to Group B and C were instructed to provide blood samples to evaluate FPG and 2-hour PPG levels prior to next scheduled visit (Visit DE 1) in a manner such that, results were available before the day of Visit DE 1

- Accountability and compliance check
  - Dispensing of subject diary to record IP and non-IP dosing details, AEs (including hypoglycaemic episodes), capillary glucose measurements, details of hypoglycaemic episode, and change in concomitant medications

Visit: Dose Escalation 1 (Visit DE 1, for Group B and Group C subjects)

This visit was conducted only for the subjects who were randomized to treatment Group B and Group C. The following study procedures and assessments were done at this visit:

- The following details were recorded at this visit:
  - Body weight (kg)
  - Recording of vital signs: SBP and DBP (mmHg), PR [beats/min], respiratory rate (RR) [breaths/min] in supine position after 5 minutes of rest and body temperature (°F)
  - Concomitant medications
  - AE/SAE, if any
- Subject diary was collected and reviewed
- Subject diary was dispensed
- Accountability and compliance check of IP:
  - Accountability check was done by recording number of capsules dispensed to the subjects (as per the dose) versus number of capsules used and/or the number of capsules lost/destroyed in the accountability log and appropriate details were transcribed from log to eCRF
  - Compliance check was done by calculating number of capsules (as per dose dispensed) consumed by the subject versus total capsules required to be consumed
- Review of FPG and PPG test result value prior to dispensing of IP
- Dispensing of IP:
  - Subjects in Group B, after reviewing the data of fasting and PP glucose, were dispensed USVCAP capsules of dose strength 150 IU BD and were prescribed 1 capsule of USVCAP (i.e. assigned fixed dose 150 IU, BD for 12 weeks) orally one hour prior to breakfast and dinner until the next scheduled visit. They were instructed to visit the study site for their next scheduled visit (Visit 3 [Day 15/+2 days])
  - Subjects in Group C, after reviewing the data of fasting and PP glucose, were dispensed USVCAP capsules of dose strength 150 IU and was prescribed 1 capsule of USVCAP (i.e. lower dose (150 IU, BD) based on the assigned fixed dose – 300

IU, BD for 12 weeks) orally twice daily one hour before breakfast and dinner until the next scheduled visit. They were instructed to provide blood samples to evaluate FPG and 2-hour PPG levels prior to next scheduled visit (Visit DE 2) in a manner, such that results were available before the day of Visit DE 2.

Visit Dose Escalation 2 (Visit DE 2, for Group C subjects only)

This visit was conducted only for subjects who are randomized to treatment Group C and have completed DE visit 1. The following study procedures and assessments were done at this visit:

- The following details should be recorded at this visit:
  - Body weight (kg)
  - Vital signs: SBP and DBP (mmHg), PR [beats/min], respiratory rate (RR) [breaths/min] in supine position after 5 minutes of rest and body temperature (°F)
  - Concomitant medications
  - AE/SAE, if any
- Subject diary was collected and reviewed
- Subject diary was dispensed at each visit
- Review of FPG and 2-hour PPG test result value prior to dispensing of IP
- Accountability and compliance check of IP
  - Accountability check was done by recording number of capsules dispensed to the subjects (as per the dose) versus number of capsules used and/or the number of capsules returned/lost/destroyed in the accountability log
  - Compliance check was done by calculating number of capsules (as per dose dispensed) consumed and number of capsules required to be consumed
- Dispensing of IP:
  - Subjects in Group C, after reviewing the data of fasting and PP glucose, were dispensed USVCAP capsules of dose strengths 150 IU and was prescribed 2 capsules of USVCAP (i.e. assigned fixed dose 300 IU, BD for 12 weeks) until next visit. Subject was instructed to visit the study site for next scheduled visit (Visit 3 [Day 22/+ 2 days])

Visit 3 to Visit 6

The following procedures and assessments were performed for all subjects in all 3 treatment groups at each visit from Visit 3 to Visit 6:

The following details should be recorded at this visit:

- Findings from physical examination
- Body weight (kg), waist circumference (cm) and body mass index (BMI) (kg/m^2)
- Vital signs: SBP and DBP (mmHg), PR [beats/min], respiratory rate (RR) [breaths/min] in supine position after 5 min of rest and body temperature (°F)
- AE/SAEs (including details of hypoglycaemic episode)
- Concomitant medications

- Subject diary was collected and reviewed at each visit (Visits 3 to 6)
- Subject diary was dispensed at each visit (Visits 3 to 6)
- Accountability and compliance check of IP
    - Accountability check was done by recording number of capsules dispensed to the subjects (as per the dose) versus number of capsules used and/or the number of capsules lost/destroyed in the accountability log
    - Compliance check was done by calculating number of capsules (as per dose dispensed) consumed by the subject versus total capsules required to be consumed
- Laboratory investigations
    - Fasting plasma glucose (at Visits 3, 4 and 6 only)
    - 2-hours postprandial plasma glucose (at Visits 3, 4 and 6 only)
- Dispensing of IP at Visits 3, 4, 5, and 6 as per the treatment groups:
    - Subjects in Group A were dispensed USVCAP capsules of dose strengths 75 IU at each visit up to Visit 6 and were prescribed 1 capsule of USVCAP (i.e. assigned fixed dose: 75 IU, BD) orally twice daily before breakfast and dinner at each scheduled visit until 1 day prior to next scheduled visit (i.e. Visit 7/Day 85 [+2 days])
    - Subjects in Group B were dispensed USVCAP capsules of dose strength 150 IU at each visit up to Visit 6 and were prescribed 1 capsule of USVCAP (i.e. assigned fixed dose: 150 IU, BD) orally twice daily before breakfast and dinner until 1 day prior to next scheduled visit (i.e. Visit 7/ Day 92 [+2 days])
    - Subjects in Group C were dispensed USVCAP capsules of dose strength 150 IU at each visit up to Visit 6 and were prescribed 2 capsules of USVCAP (i.e. assigned fixed dose: 300 IU, BD) orally twice daily before breakfast and dinner until 1 day prior to next scheduled visit (i.e. Visit 7/ Day 99 [+2 days])

Visit 7 (End-of-treatment visit)

This was the EOT visit for all subjects. It occurred on the next day after the subject had completed administration of twice daily doses of assigned fixed dose IP for 12 weeks. The following procedures and assessments were performed at this visit:

- The following details should be recorded at this visit
    - Findings of physical examination
    - Body weight (kg), waist circumference (cm), and body mass index (BMI) (kg/m^2)
    - Vital signs: SBP and DBP (mmHg), PR [beats/min], RR [breaths/min] in supine position after 5 min of rest and body temperature (°F)
    - Change in concomitant medications, if any
    - AE/SAE, (including details of hypoglycaemic episodes), if any
    - 12-lead ECG
- Subject diary was collected and reviewed
- Laboratory investigations:

- Blood samples were withdrawn from the subject to conduct the laboratory investigations at central laboratory.
  - Fasting plasma glucose
  - 2-hours PPG level
  - HbA1c level
  - Lipid profile: Total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), very low-density lipoprotein (VLDL), and triglycerides after 12 hours of fasting
  - Liver function tests: ALT, AST, ALP and total bilirubin
  - Renal function tests: Serum creatinine, BUN, sodium, potassium, chloride, and eGFR
  - Total protein & A/G ratio
  - Calcium, phosphorus, vitamin D, PTH
  - Urine samples were collected for UPT, only for females of childbearing potential or who are ≤ 1 year postmenopausal prior to enrolment
  - Insulin Antibody test - Anti insulin antibody test

Visit 8 (End-of-Study Visit)

This was the EOS visit for all subjects. It occurred at completion of 4-weeks of post-treatment follow-up per the treatment group. The following procedures and assessments were performed at this visit:

- The following details were recorded at this visit:
  - Findings from physical examination
  - Body weight (kg), waist circumference (cm), and body mass index (BMI) (kg/m^2)
  - Vital signs: SBP and DBP (mmHg), HR [beats/min], RR [breaths/min] in supine position after 5 min of rest and body temperature (°F)
  - Change in concomitant medications, if any
  - AE/SAE, (including details of hypoglycaemic episodes) if any
  - Urine samples were collected for UPT, only for females of childbearing potential or who are ≤ 1 year postmenopausal prior to enrolment
  - Insulin Antibody test - Anti insulin antibody test

Discussion of Study Design, Including Choice of Control Group

The proposed oral formulation USVCAP addresses most concerns regarding delivery of insulin through oral route. USVCAP is a formulation containing recombinant human insulin and excipients. The excipients are added to promote absorption of active drug substance in jejunum. The technology used in the unique formulation, can enhance the passage of large molecules such as peptides, and proteins across the intestinal wall from lumen into the bloodstream. The formulation is stable and is designed in such a way that the dry powder dissolves rapidly in the liquid in the small intestine, bringing all components of the formulation (including peptides) in contact with the cell wall at the same time.[11]

The rationale for combining insulin and oral drug therapy is derived from a better understanding of the pathophysiology of non-insulin dependent diabetes mellitus and of the mechanisms of action of the oral drugs:

1) T2DM subjects are both insulin-deficient and insulin-resistant, thus requiring quite high doses of exogenous insulin
2) Peripheral insulin delivery leads to hyperinsulinemia which could play a role in the pathogenesis of late diabetic complications;
3) Metformin hydrochloride (by improving glucose metabolism and insulin sensitivity) and alpha-glucosidase inhibitors (by slowing down the digestion of complex carbohydrates and sucrose) are able to reduce the amounts of insulin needed to control postprandial hyperglycaemia[15]

For subjects who fail to respond to the initial therapy, there are several agents that are available and can be used with metformin. Insulin is the preferred second-line medication for subjects with increased HbA1c or with symptoms of hyperglycaemia despite initial therapy with metformin and lifestyle intervention.[6] Most recommendations agree that if HbA1c level is > 8.5-9% irrespective of the dose of oral anti-diabetic drug (OAD), insulin should be initiated particularly in combination with metformin.[16] The consensus statement by the American Association of Clinical Endocrinologists/ American College of Endocrinology (AACE/ACE) on the comprehensive T2DM management recommends insulin doses based on HbA1c levels (HbA1c < 8%; TDD: 0.1-0.2U/kg; HbA1c >8%; TDD: 0.2-0.3U/kg).[17]

The current study was undertaken to generate evidence on the safety, efficacy and immunogenicity of USVCAP Formulation in Type 2 Diabetes Mellitus Subjects Uncontrolled with Metformin Hydrochloride Treatment in real world settings.

The safety of USVCAP formulation in Type 2 Diabetes Mellitus Subjects Uncontrolled with Metformin Hydrochloride Treatment was determined by incidence and severity of treatment emergent adverse events (TEAEs) that occurred during the study period, including occurrence of hypoglycaemic episodes in each treatment group during the study period; and change in laboratory investigations post 12-week administration of USVCAP. Efficacy of the treatment was assessed by change in glycated haemoglobin (HbA1c) level post 12-week twice daily administration of selected fixed dose of USVCAP (75 IU, or 150 IU or 300 IU) from baseline, comparison of change in HbA1c between the 3 fixed dose levels studied to examine dose response relationship post 12-week administration of USVCAP and change in FPG and 2-hour PPG levels in each treatment group post 12-week administration of USVCAP. The immunogenicity was assessed by evaluating incidence of treatment-emergent antibody response (TEAR).

Selection of Study Population

Inclusion Criteria

1. Male or female aged 35 to 60 years (both inclusive)
2. Type 2 diabetes mellitus diagnosed < 2 years prior to enrolment
3. Glycated haemoglobin level ≥ 7% and ≤ 9.5%
4. On stable oral monotherapy with metformin hydrochloride (1000 mg to 2500 mg/day) and regular diet and exercise regimen at least 12 weeks prior to enrolment
5. Body mass index between 18 to 30 kg/m2
6. Ability to perform capillary blood glucose measurements

7. Willing to provide informed and written consent for the clinical trial
8. Able to comply with all requirements of clinical trial protocol

Exclusion Criteria

1. Subject with history or evidence of hypersensitivity to insulin or metformin hydrochloride or its excipients
2. Suffering from type 1 diabetes mellitus
3. Received treatment with sulphonylureas or alphaglucosidase inhibitors, Glucagon-like peptide-1 (GLP-1) receptor agonists or Sodium-glucose co-transporter 2 (SGLT2) inhibitors or meglitinides or pramlintide or thiazolidinediones within 3 months prior to enrolment
4. Previously treated with insulin within 3 months prior to enrolment
5. History of episodes of hypoglycaemia during 3 months prior to enrolment.
6. Reduced awareness of hypoglycaemia or inability to identify and tackle hypoglycaemic episodes
7. History of substantial weight loss defined as 5% decrease in body weight within the last 6 months
8. Medical history of unstable angina within 1 year prior to enrolment
9. History of tobacco or nicotine more than two packs/day within 3 months prior to enrolment
10. Is, at the time of signing informed consent, a user of recreational or illicit drugs or has had a recent history (within 1 year prior to enrolment) of drug or alcohol abuse or dependence. (Note: Alcohol abuse includes heavy alcohol intake as defined by >3 drinks per day or >14 drinks per week, or binge drinking).
11. History of gastrointestinal disorders which may potentially interfere with absorption of the IP
12. Treatment with systemic corticosteroids or with inhalational corticosteroids (Beclomethasone or budesonide) within the 3 months prior to enrolment
13. Likelihood of requiring treatment during the study period with prohibited medications mentioned (as defined in this clinical trial protocol)
14. Female subject who is pregnant, lactating or planning pregnancy during the trial
15. Female subject of childbearing age who is not willing to use adequate method of contraception during the study period
16. Life expectancy of less than 6 months from screening
17. Elective surgery or any other surgical procedure/s requiring general anaesthesia during the clinical trial
18. Has participated in another research trial within 12 weeks prior to screening
19. History of diabetic ketoacidosis requiring hospitalization within 6 months prior toenrolment, case of proliferative retinopathy or advanced neuropathy
20. Subject having any of the following laboratory results at screening
    a. Estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2

b. Alanine aminotransferase (ALT) and/or Aspartate aminotransferase (AST) >3 times of upper limit normal

c. Blood urea nitrogen (BUN) > 30 mg/dL

21. Subject who has a positive serology for hepatitis B virus (HBV) or hepatitis C (HCV) or human immunodeficiency virus (HIV) infections at screening
22. Subject who has undergone pancreatectomy or pancreas islet transplant or renal transplant
23. Subject receiving or has received any immunomodulation medications within 1 year prior to enrolment
24. Subject with history or evidence of diabetic complications (e.g. diabetic retinopathy, diabetic neuropathy, or diabetic nephropathy, etc.), cardiac disorders, or any other systemic complication due to diabetes, which in the opinion of the Investigator signifies subjects' ineligibility for the trial
25. Has any concurrent disease or medical/surgical condition, which required treatment of more than 3 months and which in the opinion of the Investigator does not allow participation of the subject in this study.

Study Specific Discontinuation/Withdrawal Criteria

The subjects could withdraw their consent to continue participation in the study without providing any reason, or the Investigator could decide in the interest of the safety of the subject to withdraw the subject from trial at any time during the study period.

The subject was withdrawn from the study treatment or discontinued from the trial due to any one of the following reason:

- Subjects' voluntary withdrawal of consent
- Protocol violation
- Subject's non-compliance to the administration of IP as per the protocol
- Any AE or SAE requiring withdrawal of subject in the opinion of the Investigator
- Requirement of prohibited concomitant medication
- Requirement of dose reduction for both IP and non-IP
- Study termination by the Sponsor
- Study termination based on the advice by CDSCO or any other competent authority
- Subjects who experience 2 or more than 2 episodes of hypoglycaemia within a day
- Subjects diagnosed with uncontrolled hyperglycaemia as defined in the protocol

The Investigator discussed with the subject, the most appropriate way to withdraw from the study to ensure the subject's health and safety. The subject was called to visit the study site and all study assessments and procedures were performed as per the EOT visit (i.e. Visit 7) (Table 3). In case of an ongoing SAE, the subjects were followed up till recovery or stabilization of SAE, whichever was appropriate without compromising on subject's safety.

STUDY TREATMENT OF SUBJECTS

Treatment Administered

- Group A: USVCAP 75 IU, BD for 12 weeks
- Group B: USVCAP 150 IU, BD for 12 weeks
- Group C: USVCAP 300 IU, BD for 12 weeks

Investigational Product

The investigational product, USVCAP was administered at doses 75 IU, 150 IU, and 300 IU, orally, twice daily.

Dosage form: It was supplied by the sponsor as 75 IU and 150 IU capsules for oral administration.

Dosage: Each subject allocated to treatment Groups A, B, or C received treatment with USVCAP IP as follows:

For subjects randomized to Group A (USVCAP 75 IU BD for 12 weeks) administered the IP as follows:

USVCAP 75 IU BD: Day 1 until Day 84

For subjects randomized to Group B (i.e. USVCAP 150 IU BD for 12 weeks) and Group C (i.e. USVCAP 300 IU BD for 12 weeks):

There was a run-in period/s of 1 week with each lower dose/s prior to initiation of the assigned fixed dose of USVCAP (Table 2). Upon completion of the run-in period/s, the subjects received the assigned fixed dose of USVCAP further for 12 weeks.

The Investigator considered the dose increase for each subject in Group B and Group C only if there was no evidence of lack of tolerability with dose/s of IP prescribed during run-in period/s and that the safety of the subject was unlikely to be compromised after administration of subsequent higher dose/s of the IP.

The dose increase at each DE visit was considered only after laboratory test results for FPG and 2-hour PPG levels were available to the Investigator.

For subjects in Group B (USVCAP 150 IU BD for 12 weeks):

- Run-in period
  - USVCAP 75 IU BD: Day 1 until Day 7
- Treatment period
  - USVCAP 150 IU BD: Day 8 until Day 91

For subjects in Group C (USVCAP 300 IU BD for 12 weeks):

- Run-in periods
  - USVCAP 75 IU BD: Day 1 until Day 7: 75 IU BD
  - USVCAP 150 IU BD: Day 8 until Day 14
- Treatment period
  - USVCAP 300 IU, BD: Day 15 until Day 98

The USVCAP doses were administered as per the trial protocol until the EOT. The subjects were withdrawn from the trial if there was requirement for change in dose during the treatment period (including run-in period and/or assigned fixed dose period), due to any reason(s).

Mode of administration: 1 hour before breakfast and dinner, orally with water

Duration of Treatment:

Treatment period: Each subject was treated with assigned fixed dose of USVCAP (Group A or Group B or Group C) for 12 weeks.

Overall duration of treatment with IP (including run-in period/s):

- Group A=12 weeks
- Group B=13 weeks
- Group C=14 weeks

During the post-treatment follow-up period, subjects were advised treatment for T2DM as per standard treatment guidelines.

Non-investigational Product

It was metformin hydrochloride capsules 250 mg, 500 mg, 850 mg or 1000 mg doses.

Dosage: Subjects continued their pre-study oral anti-diabetic monotherapy (i.e. metformin hydrochloride) as per pre-study dose and regimen from screening until the EOT, the dose adjustment for which, was not allowed during the entire treatment period.

Mode of administration: Orally with water along with meals

Duration of Treatment

- Approximately 17-19 weeks based on the randomized treatment group (i.e. Group A, Group B, or Group C).

Treatment during Post-Treatment Follow-Up Period:

- During the post-treatment follow-up period, subjects were advised treatment for T2DM as per standard treatment guidelines

Investigational Medicinal Product Handling and Accountability

Dispensing, Packaging and Labelling

The IP was supplied by the sponsor designee/pharmacist to the sites sufficiently, as required for all the subjects. The Investigator/designee dispensed the treatment to subjects as per the randomization codes assigned by IWRS.

The dose and total number of capsule/s to be dispensed to the subject were as per the requirement of dosing at corresponding visit per each treatment group. The IP was supplied to the sites.

The label of IP included with the following information, but not limited to:

- Study Identification Code
- Kit Code
- Batch Number
- Manufacturing Date

- Expiry Date
- Dose strength of each capsule
- Quantity statement
- Direction for Use
- Storage Condition
- The statement “For Clinical Trial Use Only”
- Sponsor/Manufactured by

The label of the box containing IP included with the following information but not limited to:

- Study Identification Code
- Kit Code
- Batch Number
- Manufacturing Date
- Expiry Date
- Quantity statement
- Direction for Use
- Storage Condition
- Site Number
- The statement “For Clinical Trial Use Only”
- Sponsor/Manufactured by

Handling, Storage, and Disposal

Investigational product

The IP was not used beyond the expiration date stamped on the label/box. Do not freeze or expose to excessive heat or direct sunlight. The IP was stored between 2° to 8°C (both inclusive).

Study Drug Accountability Procedures

The Investigator was responsible for the overall conduct of the study. Under no circumstances, the Investigator allowed the IP to be used other than as directed by study protocol. An accurate record of the receipt of IP from Sponsor/designee, dispensing of the IP to subject and return/lost or destroyed IP by the subject was maintained. Upon completion of the study, the used and/or unused IP capsules and other supplies (if any) were shipped to Sponsor for storage or destruction as per sponsor’s communication.

Identity of Investigational Products

The investigational product (IP) is USVCAP Formulation a solid oral dosage form in capsules. Each capsule contains IP in dose strengths 75 IU or 150 IU.

Method of Assigning Patients to Treatment Groups

One hundred and fifty-three (153) subjects were enrolled in the study. These subjects were randomized in a ratio of 1:1:1 to receive IP from any one of the following 3 treatment groups:

- Group A: USVCAP 75 IU, BD for 12 weeks
- Group B: USVCAP 150 IU, BD for 12 weeks
- Group C: USVCAP 300 IU, BD for 12 weeks

Eligible subjects were randomly assigned to any one of the above treatment groups by a randomization code generated by an interactive web response system (IWRS).

The subjects were randomized in the study using permuted block randomization into 3 treatment groups. The randomization list was prepared using a validated computer program, statistical analysis system® (SAS®) for Windows version 9.4/Proc PLAN (SAS® Institute Inc., Cary, NC, USA). An IWRS method containing randomization codes was used to randomize the eligible subject to the treatment groups.

Selection of Doses in the Study

The investigational product, USVCAP was administered at doses 75 IU, 150 IU, and 300 IU, orally, twice daily.

Selection and Timing of Dose for Each Patient

Each subject allocated to treatment Groups A, B, or C received treatment with USVCAP IP as follows:

For subjects randomized to Group A (USVCAP 75 IU BD for 12 weeks) administered the IP as follows:

USVCAP 75 IU BD: Day 1 until Day 84

For subjects randomized to Group B (i.e. USVCAP 150 IU BD for 12 weeks) and Group C (i.e. USVCAP 300 IU BD for 12 weeks):

Therewas a run-in period/s of 1 week with each lower dose/s prior to initiation of the assigned fixed dose of USVCAP (Table 2). Upon completion of the run-in period/s, the subjects received the assigned fixed dose of USVCAP further for 12 weeks.

Blinding

Not applicable as this is an open-label study.

Maintenance of Study Treatment Randomization Codes

Final randomization list and codes are kept strictly confidential and are filed securely by the independent biostatistician. The randomization codes were accessible only to authorized persons until completion of the study.

Emergency Unblinding of an Individual Subject in the Study

Not applicable as this is an open-label study.

Medication(s)/Treatment(s) Permitted and Not Permitted Before and/or During the Study

Prior medication

All subjects were enquired for prior treatment/surgery at the time of screening:

- Surgical and medical history (including T2DM history) were recorded
- Relevant prior treatment (including and anti-diabetic treatment) was documented in the electronic case report form (eCRF).

Concomitant Medications

- All prescription and non-prescription medications received by the subjects during the study were recorded in the eCRF. Any concomitant medications/treatment taken by the subject for treatment of hypoglycaemia were also documented and recorded in the eCRF and subject diary, as appropriate.

Medications/Treatments Permitted

The following medications were permitted during the study:

- Pre-study oral monotherapy with Metformin hydrochloride (at dose and regimen and documented at screening visit)
- Any other non-prohibited medications deemed necessary for the well-being and safety of the subject was permitted. The Investigator took care that such a non-prohibited medication did not interfere the trial results. If such a medication was required, the subject was not enrolled or withdrawn from the study

Subjects with inadequate glycaemic control

Hypoglycemia: Study subject who had hypoglycaemia, needed immediate treatment for the safety of the subject. It was important for subject to recognize signs and symptoms of hypoglycemia. Subjects enrolled in the study were educated on signs and symptoms of hypoglycemia and were instructed to keep glucose tablets handy. To treat hypoglycaemia, they were instructed to immediately take 04 tablets of glucose (total 15- 20 grams of glucose).

Capillary glucose level of < 70 mg/dL indicates hypoglycaemia. The Investigator specifically instructed the subjects to perform capillary glucose measurements in case they experienced any symptoms suggestive of hypoglycaemia. Such glucose measurements were to be preferably conducted prior to treatment/management of hypoglycaemic episode.After 15 minutes of intake of glucose tablets, repeat capillary glucose measurement was to be done to check if the capillary glucose level was >70 mg/dL. If the capillary glucose level was still <70 mg/dl, then another 04 glucose tablets was be taken and capillary glucose measurement again taken after 15 minutes. Once capillary glucose level was above 70 mg/dL, the subject was required to consume a meal or snack to prevent recurrence of hypoglycaemia.

Uncontrolled hyperglycaemia: Uncontrolled hyperglycaemia was diagnosed with either capillary glucose or plasma glucose measurements.

Capillary glucose: Capillary glucose values of fasting > 95 mg/dL and 2 hours postprandial >126 mg/dL despite taking correct dose of study medication and regular diet was suggestive of uncontrolled hyperglycaemia. After a high capillary glucose measurement (as suggested above), subject was instructed to repeat capillary glucose measurements daily. After 03 consecutive abnormal capillary glucose measurement value, subject called the Investigator to inform above the high glucose levels and got his/her advice.

At each site visit, the Investigator reviewed the capillary glucose measurements recorded in the patient diary. If more than 60% of the capillary glucose measurement values taken since the last visit were more than the above stated value, then Investigator withdrawn the subject from the study and shifted to other hypoglycemic medication.

Plasma glucose: When, in two consecutive plasma glucose measurements, the following fasting plasma glucose (FPG) values were noted:

- From baseline to week 6 - >270 mg/dL

- From week 6 to week 12 - >240 mg/dL

Such subjects were withdrawn from the study & shifted to other anti-diabetic medication.

Prohibited Medications

The following were the prohibited medications during the study:

- Any anti-diabetic treatment other than pre-study oral monotherapy with metformin hydrochloride
- Systemic glucocorticoids and other drugs that are known to impact the glycaemic control
- Any other drug/therapy which could affect implementation of the protocol difficult or interpretation of the trial results.

Treatment Compliance

Subjects were asked to return used and unused capsules of IP at each visit. The number of unused capsules received at each visit during the treatment period (except Visit 2), including number of capsules destroyed or lost at each visit were recorded in the IP accountability log.

Compliance to study treatment at each visit was checked by reconciling the number of capsules required to be consumed and the number of capsules consumed at each corresponding visit.

Overall treatment Compliance was calculated in terms of percentage as:

$$\frac{\text{Number of tablets actually taken during the trial}}{\text{Total number of tablets to be taken during the trial}} \times 100$$

Efficacy and Safety Measurements Assessment

Efficacy Assessment

Glycated Haemoglobin (HbA1c), Fasting Plasma Glucose (FPG) and Postprandial Plasma Glucose

The efficacy assessments HbA1c, FPG and 2-hour PPG were assessed at the central laboratory identified for the study.

It was performed as follows:

- At screening to confirm the eligibility of the subject in the study
- During the treatment period and at EOT to evaluate to assess the safety and the treatment response
- At the EOS to evaluate the post-treatment safety of the subjects after twice daily administration of IP for 12 weeks

The blood samples for HbA1c, FPG and 2-hour PPG were withdrawn from the subject for the following tests:

- Glycated haemoglobin at Visit 1 and Visit 7
- Fasting plasma glucose level under fasting condition i.e. at least 8–10 hours of overnight fasting at Visits 1, 3, 4, 6, and 7 for all subjects

  For Group B subjects: Prior to Visit DE 1

  For Group C subjects: Prior to Visit DE 1 and Visit DE 2

- Postprandial glucose level (2-hours after meal) at Visits 1, 3, 4, 6 and 7 for all subjects.

  For Group B subjects: Prior to Visit DE 1

  For Group C subjects: Prior to Visit DE 1 and Visit DE 2

- All samples were sent to central laboratory for evaluation. FPG and 2-hour PPG test results at Visit DE 1 and Visit DE 2 should be available prior to dosing.

Capillary glucose measurements

Capillary glucose measurements were performed by the subjects using a self-monitoring blood glucose device throughout the treatment period (from Visit 2 to Visit 7), once every week (mid-week).

During run-in period(s) (from Visit 2 to DE 1 [in Group B subjects] and from Visit 2 to Visit DE 1 and from Visit DE 1 to Visit DE 2 [in Group C] subjects), capillary glucose measurements were performed at mid-week.

The capillary glucose measurements were performed at the following 4 time points:

- Fasting: After 8 hours of overnight fast
- 2-hours post-breakfast
- 2-hours post-lunch
- 2-hours post-dinner

The measurements for all 4 timepoints were performed on the same day. All capillary glucose measurements were recorded by subject in the respective visit subject diary.

Hypoglycemia

It was important for subjects in the study to recognize signs and symptoms of hypoglycemia. Subjects enrolled in the study were educated on signs and symptoms of hypoglycemia and were instructed to keep glucose tablets handy & take 4 glucose tablets (total 15 -20 grams of glucose) immediately to treat hypoglycemia, if it occurs.

Capillary glucose level of < 70 mg/dL indicates hypoglycaemia. The Investigator specifically instructed the subjects to perform capillary glucose measurements in case they experienced any symptoms suggestive of hypoglycaemia. Such glucose measurements were to be preferably conducted prior to treatment/management of hypoglycaemic episode. After 15 minutes of intake of glucose tablets, repeat capillary glucose measurement was to be done to check if the capillary glucose level was >70 mg/dL. If the capillary glucose level was still <70 mg/dl, then another 04 glucose tablets was be taken and capillary glucose measurement again taken after 15 minutes. Once capillary glucose level was above 70 mg/dL, the subject was required to consume a meal or snack to prevent recurrence of hypoglycaemia.

If more than two episodes of hypoglycemia occurred within a day (despite taking correct dose of study medication and regular diet), then the subject was advised to visit the site immediately for further medical management & was withdrawn from the trial.

Uncontrolled hyperglycemia

Capillary glucose: Fasting capillary glucose values which were more than 110% of the 1st fasting capillary glucose measurement value taken in the study, despite taking the correct dose of study medication and regular diet, was suggestive of uncontrolled hyperglycaemia. After a high capillary glucose measurement (as stated above), the subject was instructed to repeat

capillary glucose measurements daily. After 03 consecutive high fasting capillary glucose measurement value, the subject called the Investigator to inform about the high glucose levels and got his/her advice.

At each site visit, the Investigator reviewed the capillary glucose measurements recorded in the patient diary. If more than 60% of the fasting capillary glucose measurement values taken since the last visit were more than 110% of the 1st fasting capillary glucose measurement value, then Investigator took fasting plasma glucose (FPG) measurements (which could be routine as per the Schedule of Study Procedures and Assessments or additional test) and then based on the fasting plasma glucose value, decided on subject withdrawal.

Plasma glucose:

Confirmed diagnosis of uncontrolled hyperglycemia were made if the following fasting plasma glucose (FPG) values are noted:

- From baseline to week 5 - >250 mg/dL
- From week 6 to end of study - >220 mg/dL

Such subjects were withdrawn from the study & shifted to other anti-diabetic medication unless the fasting plasma glucose measurements were equal to or less than the 1st fasting plasma glucose measurement taken in the study.

Safety Measurements

Adverse Events

Definition of Adverse Event

As per ICH-GCP, an AE is defined as "any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment". An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IP, whether or not considered related to the IP (ICH E6: 1.2).

All abnormal laboratory findings should be classified as "clinically significant" or "non-clinically significant" by Investigator as per his clinical judgment. Only "clinically significant" abnormal laboratory values should be considered as an AE.

Worsening of a pre-existing medical condition (e.g. hypertension) during the study period should be considered as an AE, if there is either an increase in severity, frequency, or duration of the condition or an association with significantly worse outcome. Pre-existing conditions recorded at screening that have not worsened during the study period are not considered AEs.

Serious Adverse Event

An SAE is defined as an AE at any dose fulfils one or more of the following criteria:

- Results in death
- Is life-threatening*
- Requires hospitalization or prolongation of existing hospitalization*
- Results in persistent or significant disability/incapacity
- results in congenital anomaly/birth defect
- Is an important medical event: important medical event in the definition of "serious"

refers to those events which may not be immediately life-threatening, or result in death, or hospitalization, but from medical and scientific judgment may jeopardize the subject and/or may require medical or surgical intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization

*NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe.

- Hospitalization is to be considered 'only hospital stay' for ≥ 24 hours. The following hospitalizations should not be reported as SAEs:
- Hospitalization or prolongation of hospitalization needed for procedures required by the clinical trial protocol
- Hospitalization or prolongation of hospitalization as part of a routine procedure followed by the centre
- Hospitalization for a survey visit, annual physicals, or social reasons
- Elective (pre-planned) hospitalizations for a pre-existing condition that had not worsened from baseline (e.g. elective or scheduled surgery arranged prior to start of the study)
- Admissions not associated with an AE (e.g. social hospitalization for purposes of respite care)

Methods and Timing for Assessing, Recording and Analysing Safety Parameters

All AEs and SAEs were collected on eCRFs from the time the subject signs the ICF until the EOS. Any SAE that was ongoing at the time the subject exits the study was followed until the event was resolved or there was a satisfactory explanation, which qualified 1 of the following outcomes:

- Resolved (With residual effects or without residual effects)
- Death
- Unknown (Despite adequate follow-up)

Documentation and Reporting of Immediately Reportable Adverse Events

All SAEs were recorded from the time the subject signed the ICF in the study until the EOS. All SAEs, regardless of causal relationship were reported by the site to sponsor/CRO, the Licensing Authority i.e. the Drugs Controller General of India, and the Chairman of Ethics Committee of the site within 24 hours of occurrence through Appendix XI of Schedule Y.

- Follow-up information on an existing SAE was reported by the Investigator. Appropriate hospitalization or autopsy reports were made available, as applicable. All SAEs were followed-up until resolution (i.e., asymptomatic, stabilization of the event or death)
- The Investigator and sponsor/CRO prepared and submitted a detailed analysed report of all the SAEs to the Head of the Institution where the trial was being conducted, to the Chairman of the Ethics Committee that accorded approval for conduct of the trial and the Licensing Authority within 14 days of occurrence of SAE (as per the Appendix

XI of Schedule Y).

- If the SAE resolved after the submission of the 14 days analysed report, the Investigator and sponsor/sponsor designee prepared and submitted a second analysed report upon resolution of the SAE

Procedures for Eliciting Reports of and Reporting Adverse Event and Intercurrent Illnesses

Eliciting, Documentation and Reporting of Adverse Events

Information on AE was derived by questioning the subjects in general terms (e.g. "How do you feel?" or "How have you been feeling since the last questioning?" respectively), by subjects' spontaneous reports, by observation, or by reviewing subject's diary.

AEs were documented on the source documents and eCRFs. Trained study monitors checked the entries in the source documents. The AEs were followed-up until resolution or until its resolution or until it is judged to be permanent. If the subject was lost-to-follow up due to an AE, then the details of the AE was recorded as per the availability of the information from the subject.

The AE was transcribed to the AE eCRF-pages. The following information was recorded for each AE:

1. Description of the AE (verbatim term/diagnosis)
2. Date of onset
3. Date of resolution
4. Severity
5. Causality or relationship to the study medication
6. Seriousness
7. Action taken (with regards to IP)
8. Other action (to treat the event)
9. Outcome

Rating of Adverse Events

- The Investigator described severity, relatedness, and outcome of every AE. The severity of the AE was graded according to NCI-CTCAE version 4.0 on a five- point scale (Grade 1 to Grade 5).

The duration of the event was described by the start date and end date.

The causal relationship of an AE to the use of the IP was described in terms of related or not related to the IP, wherein related AEs included 'Certain', 'Probable' and 'Possible' and not related included 'Unlikely' and 'Unassessable.

Causality term	**Assessment criteria**

Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) • Re-challenge satisfactory, if necessary
Probable	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Re-challenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Unassessable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

The outcome of all AEs were reported based on the following definitions, independent of whether they were serious or non-serious AEs, their severity, or their relationship to the IP:

- Recovered: Fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first study related activity after the subject signed the informed consent
- Recovering: The condition is improving, and the subject is expected to recover from the event. This term should only be used when the subject has completed the study
- Recovered with sequelae: As a result of the AE, the subject suffered persistent and significant disability/incapacity (e.g. became blind, deaf, paralyzed)
- Not recovered
- Fatal
- Unknown: This term should only be used in cases where the subject is lost to follow-up

Each AE was followed to satisfactory clinical resolution.

Hypoglycaemic events

Hypoglycaemia is the most common adverse reaction associated with insulins. The importance of symptomatic awareness of hypoglycaemia was explained to the subjects. Subjects and caregivers were educated to recognize and manage hypoglycaemia. Self-monitoring of blood glucose plays an essential role in the prevention and management of hypoglycaemia. Subjects were instructed to inform the study site in case of event of hypoglycaemia. Hypoglycaemic treatment and management was recorded separately in eCRF. See Appendix 16.1.13 for details.

Vital Signs

Vitals signs, including pulse rate (beats/min), respiratory rate (breaths/min), systolic and diastolic BP (mmHg), and body temperature (°F) was recorded at every study visit in supine position after 5 min of rest. Any abnormal vital signs judged by the Investigator as 'clinically significant' (except at screening) was considered as an AE and was recorded appropriately.

Physical Examination

A complete physical examination was assessed and recorded at every study visit, except Visit DE 1 and Visit DE 2. The physical examination comprised of total body examination including, general appearance, skin, head, eyes, ear, nose, throat, cardiovascular system, respiratory system, breast examination, lymphatic system, neurological examination, gastrointestinal system, musculoskeletal system, urogenital system, and other, as applicable. Any abnormal physical examination findings judged by the Investigator as 'clinically significant' (except at screening) were considered as an AE and was recorded appropriately.

12-Lead Electrocardiogram

A standard 12-Lead ECG was performed at screening (Visit 1) and Visit 7. Interpretation of the tracing was done by the Investigator and was documented on the ECG eCRF page, appropriately. Each ECG tracing was labelled with the protocol number, subject initials (where regulations permit), subject number, date, and was kept as a source document at the study site. A photocopy or digitally scanned copy of the tracing was also stored and labelled with protocol number, subject initials (where regulations permit), subject number, date. Any abnormal findings judged by the Investigator as 'clinically significant' (except at screening) were considered as an AE and were recorded appropriately.

Laboratory Investigations

All laboratory investigations were performed at the central laboratory. During each scheduled blood collection visit, the subject should visit the study site under fasting condition i.e. at least 8 – 10 h of overnight fasting. At any time during the study (except at screening), abnormal laboratory parameters which are clinically relevant (e.g., require dose modification and/or interruption of study treatment, lead to clinical symptoms or signs, or require therapeutic intervention), whether specifically requested in the protocol or not, were recorded on the AE eCRF page.

Blood samples were withdrawn from the subjects and the following laboratory investigations were performed at central laboratory:

- At Visit 1 and Visit 7
    - Glycated haemoglobin (HbA1c)
    - Lipid profile: total cholesterol, HDL, LDL, and triglycerides after 12 hours of fasting
    - Liver function tests: ALT, aspartate AST, total bilirubin

- Renal function tests: Serum creatinine, BUN, sodium, potassium, chloride, and eGFR. Serology tests: human immunodeficiency virus, hepatitis B virus, and hepatitis C virus tests (only at Visit 1)

- At Visit 1, 7 and 8
  - Urine samples were collected for: Urine pregnancy test (UPT): Only for females of childbearing potential or who are ≤ 1 year postmenopausal prior to enrolment
- At Visits, 1, 3, 4, and 6:
  - Fasting plasma glucose level (also prior to dosing at Visit DE 1 and DE 2);
  - 2-hour PPG level (also prior to dosing at Visit DE 1 and DE 2)
- At Visit 1 only:
  - Haematology: RBCs count, Hb, platelet count, WBCs count including differential count (only at Visit 1)
  - Serology tests: human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV) tests
  - Urinalysis: routine examination (also at Visit 8)
  - Urine samples were collected for the following tests
  - At Visit 1, 7, and 8: Urine pregnancy test (UPT): Only for females of childbearing potential or who are ≤ 1 year postmenopausal prior to enrolment
  - At Visit 1 only: Urinalysis: routine examination

Any additional laboratory tests if required during the study period could be done at local accredited laboratory.

Immunogenicity Assessment: Insulin Antibody test - Anti-insulin antibody (AIA)

The immunogenicity of the IP was assessed using validated assays. Blood samples (1 x 3.5 mL) were collected at screening visit (Visit 1), End of treatment visit (Visit 7) and Post treatment follow-up visit (Visit 8) for testing presence of anti-insulin antibodies to the IP. The procedure for sample handling, storage and analysis was provided in the central laboratory manual.

Emergency Contact

In case of any emergency, the site contacted the medical monitor from the CRO. The medical monitor provided guidance in case of any emergency related to safety of the subject.

Other Study Assessment

Body Weight, Waist circumference and Body mass index

Body weight was measured at every study visit in kg. Body mass index (BMI) (kg/m^2) and waist circumference (cm) was calculated at all study visits, except Visit DE 1 and Visit DE 2.

Body mass index (BMI) was calculated by formula:

$$BMI = \frac{Weight\ (kg)}{height^2\ (m)^2}$$

Appropriateness of Measurements

All clinical measurements were performed using standard methods that were generally recognized as being reliable, accurate, and relevant.

Primary Variable(s):

Efficacy Assessment:

- Glycated haemoglobin (HbA1c)
- Fasting plasma glucose (FPG)
- 2-hour post prandial plasma glucose (2-hour PPG)

Safety Assessments:

- AEs and SAEs (serious and non-serious AEs) were collected for relatedness, severity, seriousness, and outcome, including events of hypoglycaemia were collected once the signed informed consent was obtained from the subject
- Vital signs: Pulse rate (PR), respiratory rate (RR), systolic blood pressure (BP) and diastolic BP (in supine position after 5 minutes of rest), and body temperature (at all visits)
- Physical examination 12-Lead electrocardiogram (ECG)
- Laboratory investigations:
    - Lipid profile: Total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL) very low-density lipoprotein (VLDL) and triglycerides after at least 12 hours of fasting
    - Liver function tests: ALT, AST, and total bilirubin
    - Renal function tests: serum creatinine, eGFR, sodium, potassium, chloride, and BUN
    - Urine pregnancy test (UPT): Only for female subjects who are of childbearing potential or who are ≤ 1 year postmenopausal prior to enrolment in the study.

The Investigator described severity, relatedness, and outcome of every AE. The severity of the AE was graded according to NCI-CTCAE version 4.0 on a five- point scale (Grade 1 to Grade 5).

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/Archive/CTCAE_4.0_2009-05-29_QuickReference_8.5x11.pdf

Secondary variable(s):

Immunogenicity Assessments

- Insulin Antibody test: Anti-insulin antibody (AIA)

Pharmacovigilance-Relevant Information

Not Applicable.

Data Quality Assurance

Audits and Inspections

Not applicable.

Data Handling

The Investigator maintained all documentation relating to this study. Essential documents (as defined in the ICH-GCP) are retained until at least 2-years after the last approval of a marketing application in an ICH region, and until there were no pending or contemplated marketing applications in an ICH region or at least 2-years have elapsed since the formal discontinuation of clinical development of the IP. These documents must be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by sponsor.

In any case, all study records are for at least 5 years after the completion or discontinuation of the study. The Investigator notified sponsor or its designee of any changes in the archival arrangements, including but not limited to archival at an off-site facility, transfer of ownership of the records in the event the Investigator left the site. Sponsor notified the Investigator in writing when the study-related records were no longer needed.

Statistical Methods Planned in the Protocol and Determination of Sample Size

The following is an outline of the statistical methodology that was used to report and analyse this study. A more detailed description is provided in a separate statistical analysis plan (SAP) that includes additional exploratory analysis not explicitly mentioned in the following sections.

Study Analyses Sets

The analyses was performed on the following trial populations.

- Randomized population: The randomized population consisted of all subjects who were randomized in the study
- Safety population: The safety population consisted of all subjects who were randomized and had received at least one dose of the IP.
- Full Analysis Population: The full analysis set population consists of all the subjects who are randomized into the study, received at least one dose of the IP from the assigned dose by randomization, and had at least one post baseline assessment.
- Per Protocol (PP) population: The per-protocol (PP) population was all the subjects in the FAS population who had completed the study and did not had any major protocol deviation.

Demographic and Other Baseline Characteristics

The demographic variables such as age, gender, ethnicity, body weight and height etc. and baseline status (medical history, physical exam, etc.) was summarized for both PP and full analysis populations.

The descriptive statistics for continuous variables were presented with number (n) of non-missing observations, missing observations, Mean, Standard Deviation (SD), Median, Minimum and Maximum. For categorical data, descriptive statistics were presented with number of exposed subjects, and number (N) with percentage of observations in the various categories of the endpoint, where percentage were based on the exposed subjects.

Descriptive statistics were provided for body weight, waist circumference and BMI parameters. In addition, individual results were reviewed for any treatment-emergent changes of possible clinical significance.

Prior and concomitant medications were coded using the standard WHODD dictionary prior to analysis. Counts and percentages were presented by drug class and generic term for descriptive summarization.

Efficacy Analyses

Primary Analysis

The primary endpoint was change in HbA1c level post 12-week administration of selected fixed dose of USVCAP (75 IU, or 150 IU or 300 IU) from baseline visit within each treatment group. The actual measurement of efficacy endpoint was summarized using number of subjects (n), mean, SD, median, and minimum and maximum (range) and 95% confidence interval (95% CI) for each treatment group at both baseline and EOT (End of treatment) visits along with change from baseline to EOT for each treatment group.

The statistical analysis for the primary endpoint were carried out to compare the change in HbA1c post 12-week administration of selected dose of USVCAP from baseline visit within each of the 3 dosing groups by using paired t-test.

In addition to evaluate primary efficacy within each randomly assigned groups as planned, we also evaluated a subgroup analysis on those patients who had uncontrolled hyperglycaemia and those who had not to see the robustness of the data on primary efficacy parameter.

Secondary Analysis

The secondary endpoint of comparing the change in HbA1c post 12-week administration of USVCAP from baseline between the 3-fixed dose groups to examine the dose response relationship between them; analysis of covariance (ANCOVA) with dose groups (treatment groups), visit and interaction between visit and treatment as factors and baseline HbA1c value as covariates using Proc mixed was used. ANCOVA model determined the statistically significant difference between different dose groups on change in HbA1c from baseline to 12-week treatment with USVCAP, controlling for the effect of the baseline HbA1c value as covariate. Also, applying same ANCOVA model and coefficient estimate for dose factor, further pairwise comparisons of the three experimental dose levels for change in HbA1c post 12-week treatment with USVCAP examined the dose response relationship.

Similarly, ANCOVA model were also applied to analyze the change in fasting and postprandial plasma glucose in each treatment group.

Details of the analysis were provided in statistical analysis plan.

Safety Analysis

In this trial, safety analysis was used to perform the safety population (defined above). All safety endpoints were analysed based on descriptive statistics as described above for continuous and categorical variables and presented visit wise. The analysis of safety assessments in this study included summaries of the following categories of safety data collected for each subject.

- Adverse events (AEs)
- Physical examination
- Vital signs
- 12-lead ECG
- Laboratory investigations

Adverse Events

AEs and SAEs were coded by 20.1 version of MedDRA body system and preferred term and tabulated by indicating number and percentage of subjects and number of events. All the AEs were listed and categorized as TEAE and SAE before dosing and after dosing. All AEs, which occur after the first dose of the IP, were categorized as TEAEs i.e. AEs with onset date on or after the first dose of the IP. The TEAEs were tabulated and summarized for each treatment group as; overall TEAEs experienced by subjects during the study, TEAEs experienced by subjects during run-in period/s and TEAEs experienced by subjects during treatment with actual assigned dose of IP. All AEs were collected, evaluated and tabulated by system organ class (SOC), preferred term (PT), date of onset, relationship to the test drug, seriousness, severity, frequency, action taken, and outcome for each treatment group. Narratives of all SAEs

were presented. AE were compared between treatment groups by using Chi square/Fisher's exact test.

Vital Signs

Descriptive statistics were provided by treatment group for PR, RR, systolic and diastolic BP, and body temperature, etc. The vital signs were generated by visit as absolute values and the change from baseline were recorded. In addition, individual results were reviewed for any treatment-emergent changes of possible clinical significance.

Physical Examination

Descriptive statistics were provided by treatment group for each body system and the change from baseline were also recorded.

12-Lead Electrocardiogram

Descriptive statistics were provided. In addition, individual results were reviewed for any treatment-emergent changes of possible clinical significance.

Laboratory Assessments

Descriptive statistics were provided by treatment group for each clinical laboratory parameter and the change from baseline were also recorded. In addition, individual results were reviewed for any treatment-emergent changes of possible clinical significance.

Concomitant Medications

Summary tables were provided for prior/concomitant medications in the study.

Immunogenicity analyses

Partial correlation was used to measure the relationship between the percent change in HbA1c and percent change in anti-insulin antibodies with absolute change in total insulin dose as covariate from baseline to Visit 7 and Visit 8. Change in level of serum anti-insulin antibodies from baseline to Visit 7 and Visit 8 were compared through paired t-test within each treatment arms.

Statistical Significance

The level of significance in the primary analysis were set to 5%. The analyses was performed upon completion of the main trial period. All secondary analyses were also be performed at the 5% significance level.

Replacement of Subjects

The subject who discontinued from trial/withdrawn from the study treatment were not replaced.

Withdrawn Subject Data Collection

The subject could withdraw their consent from the trial, or this could be the Investigator's decision to discontinue the subject from trial; if they decided to do so, at any time and irrespective of the reason all efforts should be made to document the reason for treatment withdrawal/discontinuation from the trial (see section 11.5.1) and this should be documented in the e-CRF.

The Investigator/designee involved in the study documented the reason for the subject withdrawal as follows:

Subject's voluntary withdrawal of consent

Subject's non-compliance to the IP: Repeated missing of study medication doses

Protocol violation: Repeated non-follow-up for safety or efficacy procedures required for the study. Protocol violation may be also considered when the subject is not included as per protocol-defined eligibility criteria.

Any AE or SAE requiring subject withdrawal in the opinion of the Investigator: An AE form must be completed. Clinically significant abnormal value not explained by a laboratory error or being not a known or abnormal value commonly observed in this type of population was also considered as an AE or SAE, and recorded on AE form as applicable.

Requirement of prohibited medication: Recording of the details of prohibited medication were completed on the concomitant medication CRF page and the subject were withdrawn from the study.

Requirement of dose reduction for both IP and non-IP: If there was requirement for change in dose of the IP (which is not mentioned in the protocol) or non-IP at any point of time during the study period, the subject were withdrawn from the study.

Study termination by Sponsor: Upon notification of the sponsor for termination of the study

Study termination based on the advice by CDSCO or any other competent authority: If the regulatory authority(ies) directly connects to the site/CRO to terminate the study, the same was immediately done by the Investigator/information were communicated to the sites. The CRO must notify the site regarding such communications. In case of communications directly reaching the Investigator, the Investigator must inform the CRO designee (e.g. study site monitor) or both Sponsor designee and CRO designee

Any, other reason: If none of the above-mentioned reasons are applicable, then the reason for subject withdrawal were mentioned; "any other reason" and the reason were specified on the eCRF page. In case of pregnancy, the subject's study treatment must permanently stop and study discontinuation and early withdrawal procedures should be conducted.

Determination of Sample Size

It was estimated that 52 evaluable subjects per dose group were needed to be enrolled in each treatment group assuming a reduction of 0.5 in HbA1c, common standard deviation (SD) of 1.0 at baseline and at Week 12 in each dose group with 90% power and 2.5% level of significance. However, 13 extra subjects, accounting for 65 subjects per group in total were enrolled into this study with an aim to compensate for an estimated drop-out rate of 20%. Thus, a total number of 195 subjects were to be randomly assigned to either of the three dose (treatment) groups in this study in the ratio of 1:1:1. The detailed description of sample size calculation is represented in the table below:

Single Mean - Paired t-test	
Pre-test mean	7.5
Post-test mean	7
Mean Difference from Pre-to Post test	0.5
Standard deviation in Pre-test	1
Standard deviation in Post-test	1
Effect size	0.5
Power (%)	90
Alpha Error	2.5
1 or 2 sided	2
Minimum required sample size for each selected fixed dose treatment	52

group	
Minimum required sample size for all three-selected fixed dose treatment groups	156
Considering 20% drop-out, required sample size for each selected fixed dose treatment group per	65
Considering 20% drop-out, required sample size for all three-selected fixed dose treatment groups	195

Missing Data

The missing observations were imputed using Last Observation Carried Forward (LOCF) appropriately.

Procedures for Reporting Deviations from Original Statistical Plan

Any post-hoc, or unplanned, analyses not identified in SAP were clearly identified in the respective clinical study report (CSR).

Change in Conduct of the Study and Planned Analysis

Changes in Conduct of the Study

Following changes were made in conduct of study due to COVID-19 pandemic and nationwide lockdown implemented by Government of India:

- The home visits were arranged by investigator sites for laboratory sampling. The samples were processed in local hospital labs or central lab's local centres.
- Due to home visit physical examination and vital sign were not performed for these subjects and protocol deviations were filed.
- Telephonic contacts by the site team was done to record the AEs, concomitant medications and subject's clinical status as an alternate option to clinical visit. The participants whose blood samples were collected (hospital visit/home visit) within the one week of window period, were considered in the per-protocol population.

For site No. 20, the protocol approval was received however site initiation visit was not done because of nation-wide lockdown by the government of India due to COVID-19 Pandemic.

Change in Planned Analysis

Not applicable.