Study ID: ASN51-105

Study Title: A Phase 1, Open-Label, Drug-Drug Interaction (DDI) Study to Assess the Effect of ASN51 on the Pharmacokinetics of a CYP3A4 Probe Substrate in Healthy Subjects.

Participant Flow

Reporting Groups

	Description
ASN51	Participants received ASN51 once daily (QD) for 14 days (Days 2 to 15), and 3 single doses of 2.5 mg midazolam on Days 1, 3, and 16.

Overall Study

	ASN51
Started	16
Completed	15
Not Completed	1
Adverse Event	1

Baseline Characteristics

Baseline Analysis Population Description

Safety population included all participants who received at least one dose of study drug.

Baseline Measures

		ASN51
Overall Number of Participants		16
Age, Continuous	Number Analyzed	16 participants
Mean (Standard Deviation) Unit of measure: years		34.8 (9.70)
Sex: Female, Male	Number Analyzed	16 participants

		ASN51
Measure Type: Count of Participants Unit of measure: participants	Female	0 0%
	Male	16 100%
Ethnicity (NIH/OMB) Measure Type: Count of Participants Unit of measure: participants	Number Analyzed	16 participants
	Hispanic or Latino	2 12.5%
	Not Hispanic or Latino	14 87.5%
	Unknown or Not Reported	0 0%
Race (NIH/OMB) Measure Type: Count of Participants Unit of measure: participants	Number Analyzed	16 participants
	American Indian or Alaska Native	0 0%
	Asian	2 12.5%
	Native Hawaiian or Other Pacific Islander	0 0%
	Black or African American	3 18.75%
	White	11 68.75%
	More than one race	0 0%
	Unknown or Not Reported	0 0%

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Maximum Plasma Concentration (Cmax) of Midazolam and 1-hydroxymidazolam With and Without the Co-administration of ASN51
Time Frame	Pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 16 hours and 16 hours post-dose on Days 1, 3 and 16

Analysis Population Description

The pharmacokinetic (PK) analysis population included all participants who provided evaluable data for the comparisons of interest. Here, “overall number of participants analyzed” signifies those participants who were evaluable for this outcome measure.

Reporting Groups

	Description
Day 1: Midazolam	All participants received single dose midazolam 2.5 mg, orally, on Day 1.
Day 3: Midazolam + ASN51	All participants received 2.5 mg midazolam along with ASN51, orally, QD on Day 3.
Day 16: Midazolam + ASN51	All participants received 2.5 mg midazolam along with ASN51, orally, QD on Day 16.

Measured Values

	Day 1: Midazolam	Day 3: Midazolam + ASN51	Day 16: Midazolam + ASN51
Overall Number of Participants Analyzed	16	16	15
Maximum Plasma Concentration (Cmax) of Midazolam and 1-hydroxymidazolam With and Without the Co-administration of ASN51 Geometric Mean (Full Range) Unit of measure: nanograms/millilitre (ng/mL)			
Cmax of Midazolam	12.3 (6.87 to 23.7)	11.4 (5.81 to 25.1)	9.42 (5.30 to 23.4)
Cmax of 1-hydroxymidazolam	3.72 (1.67 to 7.62)	3.53 (1.13 to 7.96)	3.16 (1.05 to 10.9)

2. Primary Outcome Measure:

Measure Title	Dose-normalised Cmax (Cmax/Dose) of Midazolam With and Without the Co-administration of ASN51
Time Frame	Pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 16 hours and 16 hours post-dose on Days 1, 3 and 16

Analysis Population Description

The PK analysis population included all participants who provided evaluable data for the comparisons of interest. Here, “overall number of participants analyzed” signifies those participants who were evaluable for this outcome measure.

Measured Values

	Day 1: Midazolam	Day 3: Midazolam + ASN51	Day 16: Midazolam + ASN51
Overall Number of Participants Analyzed	16	16	15
Dose-normalised Cmax (Cmax/Dose) of Midazolam With and Without the Co-administration of ASN51 Geometric Mean (Full Range) Unit of measure: nanograms/millilitre/milligram(ng/mL/mg)	4.93 (2.75 to 9.48)	4.56 (2.32 to 10.0)	3.77 (2.12 to 9.36)

3. Primary Outcome Measure:

Measure Title	Time to Reach Maximum Plasma Concentration (Tmax) of Midazolam and 1-hydroxymidazolam With and Without the Co-administration of ASN51
Time Frame	Pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 16 hours and 16 hours post-dose on Days 1, 3 and 16

Analysis Population Description

The PK analysis population included all participants who provided evaluable data for the comparisons of interest. Here, “overall number of participants analyzed” signifies those participants who were evaluable for this outcome measure.

Measured Values

	Day 1: Midazolam	Day 3: Midazolam + ASN51	Day 16: Midazolam + ASN51
Overall Number of Participants Analyzed	16	16	15
Time to Reach Maximum Plasma Concentration (Tmax) of Midazolam and 1-hydroxymidazolam With and Without the Co-administration of ASN51 Median (Full Range) Unit of measure: hours			
Tmax of Midazolam	0.500 (0.250 to 1.43)	0.500 (0.250 to 1.00)	0.533 (0.250 to 1.23)
Tmax of 1-hydroxymidazolam	0.517 (0.500 to 2.00)	0.750 (0.250 to 1.00)	0.533 (0.250 to 1.23)

4. Primary Outcome Measure:

Measure Title	Terminal Half-life (T1/2) of Midazolam and 1-hydroxymidazolam With and Without the Co-administration of ASN51
Time Frame	Pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 16 hours and 16 hours post-dose on Days 1, 3 and 16

Analysis Population Description

The PK analysis population included all participants who provided evaluable data for the comparisons of interest. Here, “overall number of participants analyzed” signifies those participants who were evaluable for this outcome measure.

Measured Values

	Day 1: Midazolam	Day 3: Midazolam + ASN51	Day 16: Midazolam + ASN51
Overall Number of Participants Analyzed	16	16	15
Terminal Half-life (T1/2) of Midazolam and 1-hydroxymidazolam With and Without the Co-administration of ASN51 Mean (Full Range) Unit of measure: hours			
T1/2 of Midazolam	4.66 (1.70 to 7.58)	3.86 (1.83 to 7.00)	4.35 (1.63 to 10.6)
T1/2 of 1-hydroxymidazolam	3.36 (0.930 to 6.00)	3.71 (0.947 to 7.50)	2.82 (1.05 to 6.08)

5. Primary Outcome Measure:

Measure Title	Terminal Rate Constant (Lambda z) of Midazolam and 1-hydroxymidazolam With and Without the Co-administration of ASN51
Time Frame	Pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 16 hours and 16 hours post-dose on Days 1, 3 and 16

Analysis Population Description

The PK analysis population included all participants who provided evaluable data for the comparisons of interest. Here, “overall number of participants analyzed” signifies those participants who were evaluable for this outcome measure.

Measured Values

	Day 1: Midazolam	Day 3: Midazolam + ASN51	Day 16: Midazolam + ASN51
Overall Number of Participants Analyzed	16	16	15

	Day 1: Midazolam	Day 3: Midazolam + ASN51	Day 16: Midazolam + ASN51
Terminal Rate Constant (Lambda z) of Midazolam and 1-hydroxymidazolam With and Without the Co-administration of ASN51 Mean (Standard Deviation) Unit of measure: 1/hours			
Lambda z of Midazolam	0.170 (0.0762)	0.202 (0.0756)	0.193 (0.0887)
Lambda z of 1-hydroxymidazolam	0.269 (0.174)	0.253 (0.172)	0.300 (0.144)

6. Primary Outcome Measure:

Measure Title	Area Under the Plasma Concentration-time Curve From Time Zero to Time of Last (AUClast) Measurable Concentration of Midazolam and 1-hydroxymidazolam With and Without the Co-administration of ASN51
Time Frame	Pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 16 hours and 16 hours post-dose on Days 1, 3 and 16

Analysis Population Description

The PK analysis population included all participants who provided evaluable data for the comparisons of interest. Here, “overall number of participants analyzed” signifies those participants who were evaluable for this outcome measure.

Measured Values

	Day 1: Midazolam	Day 3: Midazolam + ASN51	Day 16: Midazolam + ASN51
Overall Number of Participants Analyzed	16	16	15
Area Under the Plasma Concentration-time Curve From Time Zero to Time of Last (AUClast) Measurable Concentration of Midazolam and 1-hydroxymidazolam With and Without the Co-administration of ASN51 Geometric Mean (Full Range) Unit of measure: nanograms*hours/millilitre (ng*h/mL)			
AUClast of Midazolam	29.6 (16.1 to 58.3)	26.3 (13.1 to 41.2)	21.8 (15.7 to 35.2)
AUClast of 1-hydroxymidazolam	7.93 (2.97 to 14.0)	7.04 (2.07 to 17.0)	6.46 (2.34 to 12.9)

7. Primary Outcome Measure:

Measure Title	Area Under the Plasma Concentration-Time Curve From Time Zero to Infinity (AUCinf) Measurable Concentration of Midazolam and 1-hydroxymidazolam With and Without the Co-administration of ASN51
Time Frame	Pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 16 hours and 16 hours post-dose on Days 1, 3 and 16

Analysis Population Description

The PK analysis population included all participants who provided evaluable data for the comparisons of interest. Here, “overall number of participants analyzed” signifies those participants who were evaluable for this outcome measure.

Measured Values

	Day 1: Midazolam	Day 3: Midazolam + ASN51	Day 16: Midazolam + ASN51
Overall Number of Participants Analyzed	16	16	15
Area Under the Plasma Concentration-Time Curve From Time Zero to Infinity (AUCinf) Measurable Concentration of Midazolam and 1-hydroxymidazolam With and Without the Co-administration of ASN51 Geometric Mean (Full Range) Unit of measure: ng*h/mL			
AUCinf of Midazolam	31.4 (16.6 to 65.3)	27.7 (13.6 to 46.8)	23.2 (16.5 to 38.2)
AUCinf of 1-hydroxymidazolam	8.61 (3.16 to 16.1)	7.78 (2.25 to 18.1)	7.04 (2.58 to 13.5)

8. Primary Outcome Measure:

Measure Title	Dose-normalised AUC to Infinity (AUCinf/Dose) of Midazolam With and Without the Co-administration of ASN51
Time Frame	Pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 16 hours and 16 hours post-dose on Days 1, 3 and 16

Analysis Population Description

The PK analysis population included all participants who provided evaluable data for the comparisons of interest. Here, “overall number of participants analyzed” signifies those participants who were evaluable for this outcome measure.

Measured Values

	Day 1: Midazolam	Day 3: Midazolam + ASN51	Day 16: Midazolam + ASN51
Overall Number of Participants Analyzed	16	16	15

	Day 1: Midazolam	Day 3: Midazolam + ASN51	Day 16: Midazolam + ASN51
Dose-normalised AUC to Infinity (AUCinf/Dose) of Midazolam With and Without the Co-administration of ASN51 Geometric Mean (Full Range) Unit of measure: ng*h/mL/mg	12.6 (6.64 to 26.1)	11.1 (5.45 to 18.7)	9.26 (6.60 to 15.3)

9. Primary Outcome Measure:

Measure Title	Apparent Total Clearance (CL/F) From Plasma After Non-intravenous Administration of Midazolam With and Without the Co-administration of ASN51
Time Frame	Pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 16 hours and 16 hours post-dose on Days 1, 3 and 16

Analysis Population Description

The PK analysis population included all participants who provided evaluable data for the comparisons of interest. Here, “overall number of participants analyzed” signifies those participants who were evaluable for this outcome measure.

Measured Values

	Day 1: Midazolam	Day 3: Midazolam + ASN51	Day 16: Midazolam + ASN51
Overall Number of Participants Analyzed	16	16	15
Apparent Total Clearance (CL/F) From Plasma After Non-intravenous Administration of Midazolam With and Without the Co-administration of ASN51 Mean (Standard Deviation) Unit of measure: Liters/hours (L/h)	84.4 (29.9)	96.2 (36.7)	111 (25.3)

10. Primary Outcome Measure:

Measure Title	Apparent Volume of Distribution (Vz/F) After Non-intravenous Administration of Midazolam With and Without the Co-administration of ASN51
Time Frame	Pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 16 hours and 16 hours post-dose on Days 1, 3 and 16

Analysis Population Description

The PK analysis population included all participants who provided evaluable data for the comparisons of interest. Here, “overall number of participants analyzed” signifies those participants who were evaluable for this outcome measure.

Measured Values

	Day 1: Midazolam	Day 3: Midazolam + ASN51	Day 16: Midazolam + ASN51
Overall Number of Participants Analyzed	16	16	15
Apparent Volume of Distribution (Vz/F) After Non-intravenous Administration of Midazolam With and Without the Co-administration of ASN51 Mean (Standard Deviation) Unit of measure: Liters	532 (179)	497 (149)	669 (317)

11. Secondary Outcome Measure:

Measure Title	Number of Participants With Clinically Significant Abnormalities in Clinical Laboratory Parameters
Time Frame	Up to Day 26

Analysis Population Description

Safety population included all participants who received at least one dose of study drug.

Measured Values

	ASN51
Overall Number of Participants Analyzed	16
Number of Participants With Clinically Significant Abnormalities in Clinical Laboratory Parameters Measure Type: Count of Participants Unit of measure: participants	2

12. Secondary Outcome Measure:

Measure Title	Number of Participants With Clinically Significant Abnormalities in Vital Signs
Time Frame	Up to Day 26

Analysis Population Description

Safety population included all participants who received at least one dose of study drug.

Reporting Groups

Measured Values

	ASN51
Overall Number of Participants Analyzed	16
Number of Participants With Clinically Significant Abnormalities in Vital Signs Measure Type: Count of Participants Unit of measure: participants	0

13. Secondary Outcome Measure:

Measure Title	Number of Participants With Clinically Significant Abnormalities in 12-lead Electrocardiogram (ECG) Parameters
Time Frame	Up to Day 26

Analysis Population Description
Safety population included all participants who received at least one dose of study drug.

Measured Values

	ASN51
Overall Number of Participants Analyzed	16
Number of Participants With Clinically Significant Abnormalities in 12-lead Electrocardiogram (ECG) Parameters Measure Type: Count of Participants Unit of measure: participants	0

14. Secondary Outcome Measure:

Measure Title	Number of Participants With Clinically Significant Abnormalities in Physical and Neurological Examination
Time Frame	Up to Day 26

Analysis Population Description
Safety population included all participants who received at least one dose of study drug.

Measured Values

	ASN51
Overall Number of Participants Analyzed	16
Number of Participants With Clinically Significant Abnormalities in Physical and Neurological Examination Measure Type: Count of Participants Unit of measure: participants	0

15. Secondary Outcome Measure:

Measure Title	Number of Participants With Positive Columbia-Suicide Severity Rating Scale (C-SSRS) Results
Time Frame	Up to Day 26

Analysis Population Description

Safety population included all participants who received at least one dose of study drug.

Measured Values

	ASN51
Overall Number of Participants Analyzed	16
Number of Participants With Positive Columbia-Suicide Severity Rating Scale (C-SSRS) Score Results Measure Type: Count of Participants Unit of measure: participants	0

16. Secondary Outcome Measure:

Measure Title	Number of Participants With at Least One Treatment Emergent Adverse Events (TEAEs)
Time Frame	Up to Day 26

Analysis Population Description

Safety population included all participants who received at least one dose of study drug.

Measured Values

	ASN51
Overall Number of Participants Analyzed	16
Number of Participants With at Least One Treatment Emergent Adverse Events (TEAEs) Measure Type: Count of Participants Unit of measure: participants	9

Reported Adverse Events

Time Frame	Up to Day 26
Adverse Event Reporting Description	Safety population included all participants who received at least one dose of study drug.

All-Cause Mortality

	ASN51
	Affected/At Risk (%)
Total All-Cause Mortality	0/16 (0%)

Serious Adverse Events

	ASN51
	Affected/At Risk (%)
Total	0/16 (0%)

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	ASN51
	Affected/At Risk (%)
Total	9/16 (56.25%)
Eye disorders	

	ASN51
	Affected/At Risk (%)
Dry eye [A] †	1/16 (6.25%)
Gastrointestinal disorders	
Diarrhoea [A] †	1/16 (6.25%)
Dry mouth [A] †	1/16 (6.25%)
Investigations	
Alanine aminotransferase increased [A] †	2/16 (12.5%)
Musculoskeletal and connective tissue disorders	
Arthralgia [A] †	1/16 (6.25%)
Back pain [A] †	1/16 (6.25%)
Neck Pain [A] †	1/16 (6.25%)
Nervous system disorders	
Dysgeusia [A] †	1/16 (6.25%)
Headache [A] †	1/16 (6.25%)
Lethargy [A] †	7/16 (43.75%)
Skin and subcutaneous tissue disorders	
Rash [A] †	1/16 (6.25%)

†Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA 27.0