Clinical trial results:
A Phase 2b, Open-label, Multicenter, Randomized, Controlled, 2-Arm Study to Assess the Efficacy and Safety of Orally Administered NS-018 versus Best Available Therapy in Subjects with Primary Myelofibrosis, Post-Polycythemia Vera Myelofibrosis, or Post-Essential Thrombocythemia Myelofibrosis with Severe Thrombocytopenia (Platelet Count <50,000/µL)

Summary

EudraCT number	2021-000369-34
Trial protocol	PL DE IT
Global end of trial date	16 May 2024

Results information

Result version number	v1 (current)
This version publication date	
First version publication date	
Summary attachment (see zip file)	Synoptic CSR (ns-018-201-synoptic-csr.pdf)

Trial information

Trial identification

Sponsor protocol code	NS-018-201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01423851
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	NS Pharma, Inc.
Sponsor organisation address	140 East Ridgewood Avenue, Suite 280S, Paramus, New Jersey, United States, 07652
Public contact	trialinfor@nspharma.com, NS Pharma, Inc., trialinfor@nspharma.com
Scientific contact	trialinfor@nspharma.com, NS Pharma, Inc., trialinfor@nspharma.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 October 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 May 2024
Global end of trial reached?	Yes
Global end of trial date	16 May 2024
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

• To compare the efficacy of the dose of 300 mg BID of NS-018 to the Best Available Therapy (BAT), in subjects with PMF, post-PVMF, or post-ETMF with severe thrombocytopenia
• To compare the effect on MF-associated symptoms as measured by Myelofibrosis Symptom Assessment Form version 4.0 (MFSAF v4.0) to the BAT

Protection of trial subjects:

This study was conducted in accordance with the protocol and with the following:
1) Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines.
2) Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
3) Applicable laws and regulations.

Informed Consent Process
1) The Investigator or his/her representative explained the nature of the study to the subjects or their legally authorized representative and answer all questions regarding the study.
2) Subjects were informed that their participation is voluntary. Subjects or their legally authorized representative were required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
3) A copy of the ICF(s) were provided to the subject or the subject's legally authorized representative.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	13 July 2022
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Malaysia: 3
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Germany: 2
Worldwide total number of subjects	7
EEA total number of subjects	2

SYNOPTIC CLINICAL STUDY REPORT

NS Pharma, Inc.

TITLE OF THE STUDY: A Phase 2b, Open-label, Multicenter, Randomized, Controlled, 2-Arm Study to assess the Efficacy and Safety of Orally Administered NS-018 versus Best Available Therapy in Subjects with Primary Myelofibrosis, Post-Polycythemia Vera Myelofibrosis, or Post-Essential Thrombocythemia Myelofibrosis with Severe Thrombocytopenia (Platelet Count < 50,000/μL)

Protocol Number: NS-018-201

Indication Studied: Myelofibrosis

Investigational Product: NS-018 (Ilginatinib)

Study Phase: Phase 2b

Sponsor Name:

NS Pharma, Inc.
140 East Ridgewood Avenue, Suite 280S
Paramus, NJ 07652
USA

Regulatory Agency Identifying Number(s):

IND #: 109286
EudraCT #: 2021-000369-34

Study Period 31 January 2023 to 16 May 2024

Version Number: 1.0

Date of Version: 02OCT2024

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Abbreviations

Abbreviation	Definition
AE	Adverse event
BAT	Best available therapy
BID	Twice daily
CR	Complete response
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic clinical report form
EQ-5D-5L	5-level EQ-5D version
ETMF	Essential thrombocythemia myelofibrosis
Hgb	Hemoglobin
IWG-MRT	International Working Group for Myelofibrosis Research and Treatment
JAK	Janus kinase
pRBC	Packed Red Blood Cells
PD	Progressive disease
PMF	Primary myelofibrosis
PR	Partial response
PROMIS	Patient-Reported Outcomes Measurement Information System
PT	Preferred term
PVMF	Polycythemia vera myelofibrosis
QD	Every day
QoL	Quality of Life
MFSAF v.4.0	Myelofibrosis Symptom Assessment Form version 4.0
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
RBC	Red blood cell
SAP	Statistical analysis plan
SD	Stable disease
SD	Standard deviation
SF 7B	Fatigue Short Form
SOC	System organ class

Abbreviation	Definition
SOP	Standard operating procedure
STAT3	Signal transducer and activator of transcription 3
TEAE	Treatment-emergent adverse event
TMF	Trial Master File
V.	Version

1.0 Purpose:

The purpose of this Phase 2b, open-label, multicenter, randomized, controlled, 2-arm study in subjects with primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (post-PVMF) or post-essential thrombocythemia myelofibrosis (post-ETMF) was to compare the efficacy and safety of NS-018 versus the best available therapy (BAT). The protocol and statistical output relevant to this synoptic clinical study report (CSR) are appended to the text.

In addition, to measuring changes in symptoms post-therapy, the Myelofibrosis Symptom Assessment Form, version 4.0 (MFSAF v. 4.0 in Appendix C) was used to measure self-reported changes in symptoms. Subjects were stratified at baseline by spleen volume and by history of prior Janus Kinase (JAK) inhibitor treatment and randomized to receive either NS-018 or BAT (control group). The stratification factors were as follows: 1) spleen volume ($\geq$2000 cm^3 vs <2000 cm^3); and 2) JAK inhibitor (naïve vs prior treatment). There was no MF-directed treatment (other than JAK inhibitor) for at least 2 weeks prior to initiation of NS-018 or BAT.

The original protocol and protocol amendments (n=2) are appended to this Synoptic CSR in Appendix C.

The study was terminated early on March 15, 2024, by the sponsor for business reasons. A copy of the termination letter is available on file in the Trial Master File (TMF) and appended to this Synoptic CSR in Appendix D.

2.0 Background:

Myelofibrosis (MF) may appear de novo as PMF or secondary to polycythemia vera (PV) or essential thrombocythemia (ET) as PVMF or ETMF. Approximately 90% of subjects with MF carry mutations in any of the 3 driver genes: Janus kinase 2 (JAK2) in approximately 60% of cases, calreticulin in approximately 20%, and myeloproliferative leukemia virus oncogene in approximately 10% (Shammo JM et al. 2016, Vannucchi AM et al. 2013). Mutant proteins activate the JAK/signal transducers and activators of transcription pathway and other pathways downstream, leading to myeloproliferation, proinflammatory cytokine expression, and bone marrow remodeling. (Palandri F et al. 2018, de Freitas RM et al 2018).

Both ET and PV are BCR ABL-negative myeloproliferative neoplasms (MPN). The disease of MF is so rare that accurate estimates of the incidence and prevalence are difficult for scientific epidemiologists to approximate from all available worldwide resources. A research group attempting to estimate its epidemiology approximate that the prevalence range of MF is 0.1 per 100,000 people per year to 1 per 100,000 people per year. (Moulard O et al. 2014).

With the low global and country incidence of each type of MF, recruiting for a clinical trial was not easy. Hence, the study was terminated early (March 15, 2024) for business reasons. At the time of study termination, 44% (7/16) of subjects consented were enrolled and randomized to

one of the two study arms. The following synoptic clinical study report (CSR) highlights the objectives and outcomes (primary and secondary) measures, brief study design, and the final disposition and safety measures of the subjects at study termination.

3.0 Objectives and Endpoints:

The objectives and endpoints for Study NS-018-201 are provided in Table 1.

Table 1 Clinical Objectives and Endpoints

Objectives	Endpoints
Primary	
• To compare the efficacy of the dose of 300 mg BID of NS-018 to the Best Available Therapy (BAT), in subjects with PMF, post-PVMF, or post-ETMF with severe thrombocytopenia • To compare the effect on MF-associated symptoms as measured by Myelofibrosis Symptom Assessment Form version 4.0 (MF-SAF v4.0) to the BAT	• Proportion of subjects who achieve ≥35% reduction in spleen volume from baseline to Week 24 as measured by MRI (or by CT for applicable subjects) • Proportion of subjects who achieve ≥50% reduction in total symptom score from baseline to Week 24 as measured by the MF-SAF v4.0
Secondary	
• To compare the best splenic response of 300 mg BID of NS-018 to the BAT • To compare the safety of 300 mg BID of NS-018 to the BAT	• Proportion of subjects who achieve ≥35% reduction in spleen volume from baseline at any time up to Week 24 as measured by MRI (or by CT for applicable subjects) • Comparison of the safety of NS-018 versus BAT
Exploratory	
• To evaluate the effect of NS-018 on fatigue	• Improvement in fatigue as measured by Patient-Reported Outcomes Measurement Information System (PROMIS) Fatigue Short Form (SF) 7b
• To evaluate the effect of NS-018 on health-related quality of life (QoL) and utility using the EQ-5D-5L	• Change on health-related QoL and utility using EQ-5D-5L
• To evaluate plasma PK of NS-018 in the study population	• Plasma concentration of NS-018
• To evaluate the effect of NS-018 on a bone marrow fibrosis	• Improvement of bone marrow fibrosis
• To evaluate the effect of NS-018 on phosphorylation of STAT3	• Inhibition of phospho-STAT3
• To evaluate efficacy, as measured by the rates of complete response (CR), partial response (PR), clinical improvement, stable disease (SD),	• Rates of CR, PR, clinical improvement, SD, PD and relapse as measured by the IWG-MRT response criteria

Objectives	Endpoints
progressive disease (PD) and relapse, based on the IWG-MRT response criteria	
• To evaluate the effect of NS-018 on platelet • To evaluate the effect of NS-018 on RBC	• Proportion of subjects with platelet count of ≥50,000/μL at Weeks 12 and 24
• To evaluate the effect of NS-018 on transfusion	• Proportion of platelet transfusion-independent subjects at baseline with improvement in grade of thrombocytopenia at Week 24 • Proportion of transfusion-dependent subjects at baseline who achieve transfusion independence and 50% reduction in transfusion rate at Week 24 • Improvement in platelet count without transfusion at Week 24 • Rate of RBC transfusion through Week 24 (defined as the average number of RBC units/subject/month) • RBC transfusion independence rate at Week 24 • RBC transfusion dependence rate at Week 24 • Improvement in hemoglobin level without transfusion at Week 24
• To explore changes in the expression profile of mRNA by NS-018 versus baseline assessment	• Change of mRNA expressions by using mRNA sequencing
• To evaluate the splenic response and the effect on improvement of MF-associated symptoms and fatigue up to Week 48	• Improvement in splenic response, MF-associated symptoms and fatigue up to Week 48 by NS-018
• To evaluate the splenic response and the effect on improvement of MF-associated symptoms and fatigue after transitioning from BAT to NS-018	• Improvement in splenic response, MF-associated symptoms and fatigue by NS-018 after transitioning from BAT to NS-018

Abbreviations: BAT=Best Available Therapy; BID=twice daily; CR=complete response; CT=computed tomography; ETMF=essential thrombocythemia myelofibrosis; mRNA=messenger ribonucleic acid; IWG-MRT=International Working Group for Myelofibrosis Research and Treatment; MF=myelofibrosis; MF-SAF v4.0=Myelofibrosis Symptom Assessment Form version 4.0; MRI=magnetic resonance imaging; PD=progressive disease; PMF=primary myelofibrosis; PR=partial response; PVMF=polycythemia vera myelofibrosis; QoL=quality of life; RBC=red blood cell; SD=stable disease.

4.0 Design:

This study was a Phase 2b open-label, multicenter, randomized, controlled, 2-arm study in subjects with PMF, post-PVMF, or post-ETMF to compare the efficacy and safety of NS-018 versus BAT. Subjects were stratified at baseline by spleen volume and by history of prior JAK inhibitor treatment and randomized to receive either NS-018 or BAT (control group). The stratification factors were as follows: 1) spleen volume ($\geq$2000 cm^3 vs <2000 cm^3); and 2) JAK inhibitor (naïve vs prior treatment). There was no MF-directed treatment (other than JAK inhibitor) for at least 2 weeks prior to initiation of NS-018 or BAT. A total of 120 subjects were expected to be enrolled and randomized 1:1 to either NS-018 or BAT.

4.1.1 Number of Subjects

The original planned sample size was 120 subjects. Of the 16 (16/16, 100%) subjects who signed the informed consent document, 9 (9/16, 56%) subjects were screen failures, and 7 (7/16, 44%) subjects were randomized, 5 (5/16, 31%) subjects to NS-018 and 2 (2/16, 12.5%) subjects to BAT. (Table 3)

4.1.2 Disposition, demographics, and other Pertinent Baseline Characteristics

Two (2/5, 40%) out of the 5 subjects in NS-018-201 study had a history of previous JAK therapy at baseline. None of the subjects (7/7, 100%) in the study were classified as transfusion dependent at baseline. Table 2, Appendix A).

A summary of the subject Demographics and Baseline Characteristics of the Study Population are provided in Table 2.

Table 2 Summary of Baseline Demographics and Subject Characteristics

	NS-018 N=5 n (%)	BAT N=2 n (%)	Overall N=7 n (%)
Age (Years)			
n	5	2	7
Mean (SD)	65.0 (16.48)	70.5 (0.71)	66.6 (13.72)
Median	72.0	70.5	71.0
Min, Max	47, 83	70, 71	47, 83
Age Group (Years) – n (%)			
18-65	2 (40)	0 (0)	2 (29)
>65	3 (60)	2 (100)	5 (71)
Sex at Birth - n (%)			
Male	2 (40)	1 (50)	3 (43)
Female	3 (60)	1 (50)	4 (57)
Of Childbearing Potential	0 (0)	0 (0)	0 (0)
Post-menopausal	3 (100)	1 (100)	4 (100)
Premenarchal	0 (0)	0 (0)	0 (0)
Sterilized	0 (0)	0 (0)	0 (0)
Ethnicity - n (%)			
Hispanic or Latino	0 (0)	0 (0)	0 (0)
Not Hispanic or Latino	5 (100)	2 (100)	7 (100)
Not Reported	0 (0)	0 (0)	0 (0)
Race - n (%)			
American Indian or Alaska Native	0 (0)	0 (0)	0 (0)
Asian	3 (60)	0 (0)	3 (43)

	NS-018 N=5 n (%)	BAT N=2 n (%)	Overall N=7 n (%)
Black or African American	0 (0)	0 (0)	0 (0)
Native Hawaiian or Other Pacific Islander	0 (0)	0 (0)	0 (0)
White	2 (40)	2 (100)	4 (57)
Not Reported	0 (0)	0 (0)	0 (0)
Weight (kg)			
n	5	0	5
Mean (SD)	69.1 (10.68)	0	69.1 (10.68)
Median	70.0	0	70.0
Min, Max	52, 82	0	52, 82
ECOG status - n (%)			
0	1 (20)	1 (50)	2 (29)
1	4 (80)	1 (50)	5 (71)
2	0 (0)	0 (0)	0 (0)
3	0 (0)	0 (0)	0 (0)
4	0 (0)	0 (0)	0 (0)
Not Reported	0 (0)	0 (0)	0 (0)
Spleen Volume as Randomized - n (%)			
Less than 2000 cm^3	3 (60)	1 (50)	4 (57)
Greater than or equal to 2000 cm^3	2 (40)	1 (50)	3 (43)
History of Prior JAK Inhibitor Treatment as Randomized - n (%)			
Naive	3 (60)	2 (100)	5 (71)
Prior JAK Inhibitor-Treated	2 (40)	0 (0)	2 (29)
Spleen Volume at Baseline - n (%)			
Less than 2000 cm^3	3 (60)	1 (50)	4 (57)
Greater than or equal to 2000 cm^3	2 (40)	1 (50)	3 (43)
History of Prior JAK Inhibitor Treatment at Baseline - n (%)			
Naive	3 (60)	2 (100)	5 (71)
Prior JAK Inhibitor-Treated	2 (40)	0 (0)	2 (29)
Transfusion Dependence Status at Baseline n (%)			
Yes	0	0	0
No	5 (100)	2 (100)	7 (100)

Source: Table 14.1.3.2, Appendix A.

Safety Population: All randomized subjects receive at least one dose of the study treatment. This includes all BAT patients, and all subjects are analyzed as treated. (SAP V.1.0 31-May-2023 pg. 23.)

Of the 7 subjects, 5 (5/5, 100%) in the NS-018 group had a mean age of 65.0 (SD,16.48) and 2 (2/2, 100%) in the BAT group had a mean age of 70.5 (SD, 0.71). Five (71%) of the 7 subjects were > 65 years of age, and 4 (57%) of the 7 subjects were female. All subjects were identified as non-Hispanic or Latino with 4 (4/7, 57%) identified as White and 3 (3/7, 43%) identified as Asian. (Table 2)

The Eastern Cooperative Oncology Group (ECOG) performance status of all subjects (7/7, 100%) enrolled in the study was ≤ 1 with most of the subjects having a baseline ECOG score of 1 (5 [71%]: 4 [80%] in NS-018 group and 1 [50%] in the BAT group). At baseline, 2 (29%) out of the 7 subjects had previous therapy of a JAK inhibitor. (Table 2)

Table 3 Summary of Subject Enrollment and Disposition

	NS-018	BAT	Overall
Subjects Signed Informed Consent Form			16
Screen Failures			9 (56)
Subjects Randomized	5	2	7
Completed Study	0 (0)	0 (0)	0 (0)
Completed Cycle 7 Day 1 Follow-Up (Primary Endpoints)	2 (40)	2 (100)	4 (57)
Discontinued Study Treatment	5 (100)	2 (100)	7 (100)
Primary Reason for Discontinuation from Study Treatment			
Adverse Event	1 (20)	0 (0)	1 (14)
Death	0 (0)	0 (0)	0 (0)
Subject Non-Compliance/Protocol Violation	0 (0)	0 (0)	0 (0)
Physician Decision	0 (0)	0 (0)	0 (0)
Pregnancy	0 (0)	0 (0)	0 (0)
Protocol Defined Disease Progression	1 (20)	0 (0)	1 (14)
Study Terminated by Sponsor	1 (20)	0 (0)	1 (14)
Subject Withdrawal of Consent	1 (20)	0 (0)	1 (14)
Lost to Follow-Up	0 (0)	0 (0)	0 (0)
Other	1 (20)	2 (100)	3 (43)
Discontinued Study	5 (100)	2 (100)	7 (100)
Primary Reason Subject Discontinued Study			
Adverse Event	1 (20)	0 (0)	1 (14)
Death	0 (0)	0 (0)	0 (0)
Subject Non-Compliance/Protocol Violation	0 (0)	0 (0)	0 (0)
Physician Decision	0 (0)	0 (0)	0 (0)
Pregnancy	0 (0)	0 (0)	0 (0)
Protocol Defined Disease Progression	0 (0)	0 (0)	0 (0)
Study Terminated by Sponsor	2 (40)	2 (100)	4 (57)

	NS-018	BAT	Overall
Subject Withdrawal of Consent	1 (20)	0 (0)	1 (14)
Other	1 (20)	0 (0)	1 (14)

Source Table 14.1.1, Appendix A

Of the 16 subjects who signed the informed consent form, 9 (9/16, 56%) subjects were screen failures (not randomized and not treated) while 7 subjects were randomized. Of the 7 subjects, 5 (5/7, 71%) were randomized to NS-018, while 2 (2/7, 29%) subjects were randomized to BAT. Two (2/7, 29%) subjects from the BAT group transitioned to NS-018 at Cycle 7 Day 1. No subjects completed the full study, however 4 (57%) subjects completed Cycle 7 Day 1 and follow-up. Two subjects from each study group of NS-018 (2/5, 40%) and BAT (2/2, 100%) comprised those 4 (4/7, 57%) subjects. (Table 3)

In the BAT group, 2 (100%) subjects were discontinued for other reasons. No subjects were lost to follow-up or any deaths during the trial. (Table 3)

Fifty-seven percent (n=4/7) of subjects discontinued the study when the Sponsor terminated the study early. The range of days in the study for all randomized subjects was 67 to 281 for the NS-018 group and 290 to 380 days for the BAT group. (Table 3)

All subjects (7/7, 100%) discontinued study treatment for various reasons. Of the 5 (5/5,100%) subjects in the NS-018 group, one (1/5, 20%) subject discontinued because of protocol defined disease progression, one (1/5, 20%) subject withdrew their consent, one (1/5, 20%) subject ended the study because the study was terminated, one (1/5, 20%) subject discontinued because of an adverse event (AE) , and one (1/5, 20%) subject discontinued the study for other reason. A narrative of the subject that discontinued study because of worsening anemia reported as a nonserious AE is included below:

Narrative: 3107-001, 75-year-old male, Malaysia.

Subject 3107-001 was a 75-year-old Malaysian male (born 1948) who was diagnosed with MF on 28JUN2016. His primary symptoms were splenomegaly. During an in-clinic visit on the day of screening (21JUN2023), he signed the informed consent for the study prior to screening. Initial blood work at screening (21JUN2023, Day -20) revealed CTCAE Grade 3 worsen anemia with hemoglobin (hgb) reading of 72 g/L (normal level being 130-177 g/L). The following day (22JUN2023) after screening, the subject received 2 units of packed red blood cells (pRBCs). The subject was randomized to receive NS-018. At the time of the subject's baseline study visit (11JUL2023, Day 1), his hgb was at 60 g/L. The subject commenced with NS-018 at a dose of 300 mg BID (600 mg OD) on 11JUL2023 (Day 1). By Cycle 3 (04SEPT2023), the subject continued to be on NS-018 at a dose of 600 mg OD and blood work revealed ongoing CTCAE Grade 3 worsen anemia with hgb at 62 g/L. The dose of NS-018 was reduced to 400 mg OD on 06OCT2023. By 17NOV2023, his dose was further reduced to 200 mg OD. Over the course of the study, to manage his Grade 3 anemia, the subject received 28 units in total of pRBC transfusions with the last transfusion of 2 units of pRBCs on 16JAN2024. By 29JAN2024, the

subject discontinued the study. This event was considered nonserious by the PI. The subject had not recovered when he discontinued the study.

4.1.3 Safety:

All safety data was summarized by treatment at the time of the event and is provided in Table 4 and in Table 5.

All adverse events (AEs) among treated (NS-018) and BAT subjects were captured in the eCRF. AEs were classified using standard terminology from the verbatim description and according to the MeDRA dictionary, Version 24.1. The Coding dictionary assigned a system organ class (SOC) and preferred term (PT) for each event. A serious adverse event (experience) or reaction is an untoward medical occurrence that at any dose results in death or is life-threatening. (ICH E2A, 1994). Safety reporting followed all applicable external laws, regulatory requirements, and internal Standard Operating Procedures (SOPs).

A summary of TEAEs greater than or equal to Grade 3 according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 experienced by subjects over the course of the study is provided in Table 4.

Table 4 Summary of Treatment Emergent Adverse Events ≥ Grade 3 by System Organ Class and Preferred Term

System Organ Class (SOC) MedDRA Preferred Term (PT)		Number of Subjects by Randomization		
		NS-018 N=5 n (%)	BAT N=2 n (%)	Overall N=7 n (%)
Blood and Lymphatic System Disorders	anemia	3 (60)	0	3 (43)
Investigations	platelet count decreased	2 (40)	0	2 (29)
	ECOG status worsened	1 (20)	0	1 (14)
Eye disorders	Conjunctival hemorrhage	1 (20)	0	1 (14)
Gastrointestinal disorders	hematochezia	1 (20)	0	1 (14)
Infections and Infestations	influenza	1 (20)	0	1 (14)
	tracheobronchitis	1 (20)	0	1 (14)
Injury, poisoning and procedural complications	Allergic transfusion reaction	1 (20)	0	1 (14)

System Organ Class (SOC) MedDRA Preferred Term (PT)		Number of Subjects by Randomization		
		NS-018 N=5 n (%)	BAT N=2 n (%)	Overall N=7 n (%)
Metabolism and nutritional disorders	hyperglycemia	1 (20)	0	1 (14)
Respiratory, thoracic and mediastinal disorders	Chronic obstructive pulmonary disease	1 (20)	0	1 (14)

Source: Table 14.3.1.3.1, Appendix A BAT = Best Available Therapy. CTCAE v.5, the Common Technology Criteria for Adverse Events is a descriptive terminology which can be utilized for AE reporting. A grading (severity) scale is provided for each AE term. Grade 1: mild; Grade 2: moderate; Grade 3: Severe or medically significant; Grade 4: Life-threatening consequences; Grade 5: Death related to the AE.

The most common TEAE (experienced ≥ Grade 3 by preferred term (PT)) was anemia with 3 (60%) of subjects in the NS-018 group. No subjects in the BAT group had any TEAE that met the criteria of Grade 3. The second most frequently experienced TEAE was a decreased platelet count experienced by 2 (40%) subjects in the NS-018 group. The remaining TEAEs in the NS-018 group occurred in individual subjects. The PTs for these were conjunctival hemorrhage, hematochezia, influenza, tracheobronchitis, allergic transfusion reaction, worsening of ECOG score, hyperglycemia and chronic obstructive pulmonary disease. (Table 4).

A summary of TEAEs occurring in greater than or equal to 10% of all subjects by SOC and PT are provided in Table 5.

Table 5 Summary of Treatment Emergent Adverse Events Occurring in ≥ 10% of all Subjects by Subject Organ Class and Preferred Term

System Organ Class (SOC) MedDRA Preferred Term (PT)		NS-018 N=5 n (%)	BAT N=2 n (%)	Overall N=7 n (%)
Blood and Lymphatic System Disorders	anemia	4 (80)	0	4 (57)
Eye disorders	Conjunctival hemorrhage	1 (20)	1 (50)	2 (29)
	Eyelid function disorders	0	1 (50)	2 (29)
Gastrointestinal disorders	Abdominal pain	1 (20)	1 (50)	2 (29)
	Diarrhea	2 (40)	0	2 (29)
	Constipation	1 (20)	0	1 (14)

System Organ Class (SOC) MedDRA Preferred Term (PT)		NS-018 N=5 n (%)	BAT N=2 n (%)	Overall N=7 n (%)
	Hematochezia	1 (20)	0	1 (14)
	Nausea	1 (20)	0	1 (14)
General disorders and administration site conditions	Fatigue	1 (20)	0	1 (14)
	Influenza like illness	1 (20)	0	1 (14)
	Oedema peripheral	1 (20)	0	1 (14)
Hepatobiliary disorders	Cholestasis	1 (20)	0	1 (14)
Infections and Infestations	Influenza	2 (40)	0	2 (29)
	Upper respiratory tract infection	2 (40)	0	2 (29)
	Bronchitis	1 (20)	0	1 (14)
	Gastroenteritis	0	1 (50)	1 (14)
	Lower respiratory tract infection	0	1 (50)	1 (14)
	tracheobronchitis	1 (20)	0	1 (14)
	Urinary tract infection	1 (20)	0	1 (14)
Injury, poisoning and procedural complications	Allergic transfusion reaction	1 (20)	0	1 (14)
	Periorbital hemorrhage	1 (20)	0	1 (14)
	Transfusion reaction	1 (20)	0	1 (14)
Investigations	platelet count decreased	2 (40)	0	2 (29)
	C-reactive protein increased	1 (20)	0	1 (14)
	ECOG status worsened	1 (20)	0	1 (14)
Metabolism and nutritional disorders	hyperglycemia	1 (20)	0	1 (14)
	hypokalemia	2 (40)	1 (50)	3 (43)
Musculoskeletal and connective tissue disorders	arthralgia	1 (20)	0	1 (14)
	Neck pain	1 (20)	0	1 (14)
	Pain in extremity	1 (20)	0	1 (14)
	Spinal pain	1 (20)	0	1 (14)
Nervous System Disorders	lethargy	1 (20)	0	1 (14)

System Organ Class (SOC) MedDRA Preferred Term (PT)		NS-018 N=5 n (%)	BAT N=2 n (%)	Overall N=7 n (%)
	Neuropathy peripheral	0	1 (50)	1 (14)
Psychiatric Disorders	Affective disorder	0	1 (50)	1 (14)
	Insomnia	0	1 (50)	1 (14)
Renal and Urinary Disorders	Nocturia	1 (20)	0	1 (14)
Respiratory, thoracic and mediastinal disorders	Chronic obstructive pulmonary disease	1 (20)	0	1 (14)
	Cough	0	1 (50)	1 (14)
	Dyspnea	1 (20)	0	1 (14)
	Epistaxis	1 (20)	0	1 (14)
Skin and subcutaneous tissue disorders	Petechiae	1 (20)	0	1 (14)
	Skin hemorrhage	1 (20)	0	1 (14)
	Skin ulcer	1 (20)	0	1 (14)
Vascular disorders	Hematoma	1 (20)	0	1 (14)
	Venous hemorrhage	1 (20)	0	1 (14)

Source: Table 14.3.1.3.2, Appendix A, BAT = best available therapy

The most common TEAE occurring in ≥ 10% of all subjects by PT was anemia (n=4, 80%), diarrhea (n=2, 40%), influenza (n=2, 40%), upper respiratory tract infection (n=2, 40%), decreased platelet count (n=2, 40%) and hypokalemia (n=2, 40%) in the NS-018 group. (Table 5)
There was one serious TEAE (tracheobronchial event) which was considered unrelated, the subject recovered within 17 days and continued treatment 3 the study was terminated by the Sponsor. (Table 5; Listing 16.2.33, Appendix B)
No subject was lost to follow-up. (Table 3) and there were no deaths during the study. (Listing 16.2.4, Appendix B)

5.0 Conclusion:

This was a Phase 2b open-label multi-center randomized, controlled, 2-arm study to assess the efficacy and safety of orally administered NS-018 versus BAT in subjects with primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis with severe thrombocytopenia (platelet count <50,000/μL). No definitive conclusions can be made since the study was terminated early for business reasons after enrolling

in 7 subjects over a 16-month period. This includes efficacy and safety, although no subject was lost to follow-up or died during the trial. There was one serious TEAE (tracheobronchial event) which was considered unrelated, the subject recovered and continued treatment until the study was terminated by the Sponsor.