octapharma

ABBREVIATED STUDY REPORT FOR NON-INTERVENTIONAL STUDY

Immune Tolerance Induction in Hemophilia A Patients using Wilate® or Nuwiq® – A Canadian Study (WIL-26)

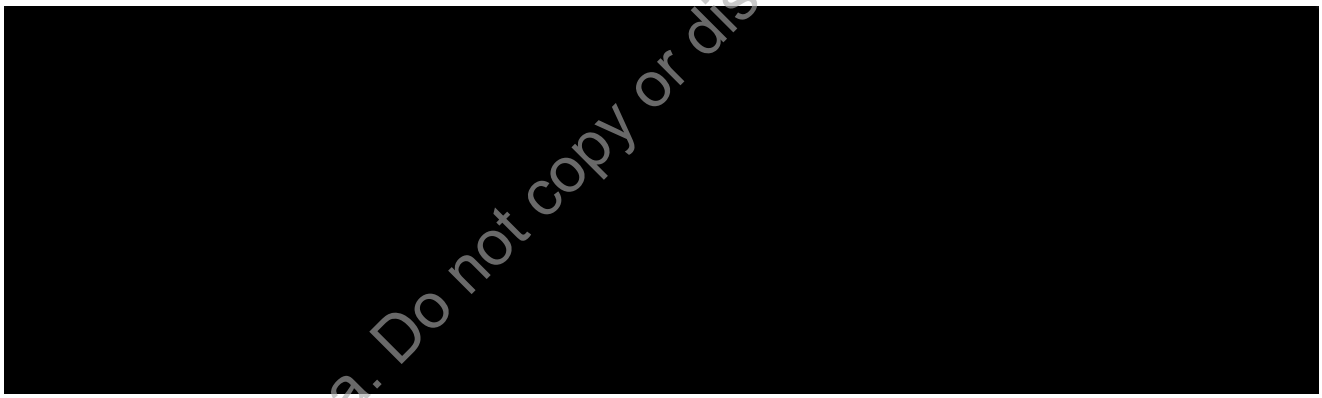
Version of the final study report	V1.0
Date of last version of report	08-Oct-2021
Study number	WIL-26
EU PAS register number	Not applicable
Active substance	Human von Willebrand factor (VWF)/human coagulation factor VIII (FVIII) Recombinant factor VIII (rFVIII)
Medicinal product	Wilate® (VWF/FVIII) or Nuwiq® (rFVIII)
Joint PASS	Not applicable
Research question and objectives	This uncontrolled, multi-centre, non-interventional study with a prospective and a retrospective cohort aimed to investigate the efficacy and safety of *Wilate* and *Nuwiq* in immune tolerance induction (ITI). The primary objective of this study was to evaluate the efficacy of *Wilate* or *Nuwiq* in achieving complete or partial ITI success in severe, moderate and mild hemophilia A patients with inhibitors. The secondary objectives of this study were to evaluate the time to achieve immune tolerance to FVIII with ITI treatment using *Wilate* or *Nuwiq*, to evaluate the bleeding frequency while on *Wilate* or *Nuwiq* ITI treatment and to evaluate the relapse rate and time to relapse following successful ITI using *Wilate* or *Nuwiq*. The additional objectives of this study were to record the patients' general and hemophilia-specific quality of life, inhibitor biology (i.e., epitope mapping, IgG subclasses, antibody binding affinity), thrombin generation assay (TGA), and genotyping.

Country of study	Canada
Sponsor's Medically Responsible Person	[redacted]
Coordinating Investigators	[redacted]
Marketing authorisation holder(s)	Octapharma AG Seidenstrasse 2 8853 Lachen Switzerland
MAH contact person	Not applicable

REPORT SIGNATURE

Signature of Octapharma's Qualified Person Pharmacovigilance or Delegate

Signature of the Sponsor's responsible global Medical Person



Signature of the Project Manager at Octapharma Responsible for the Study

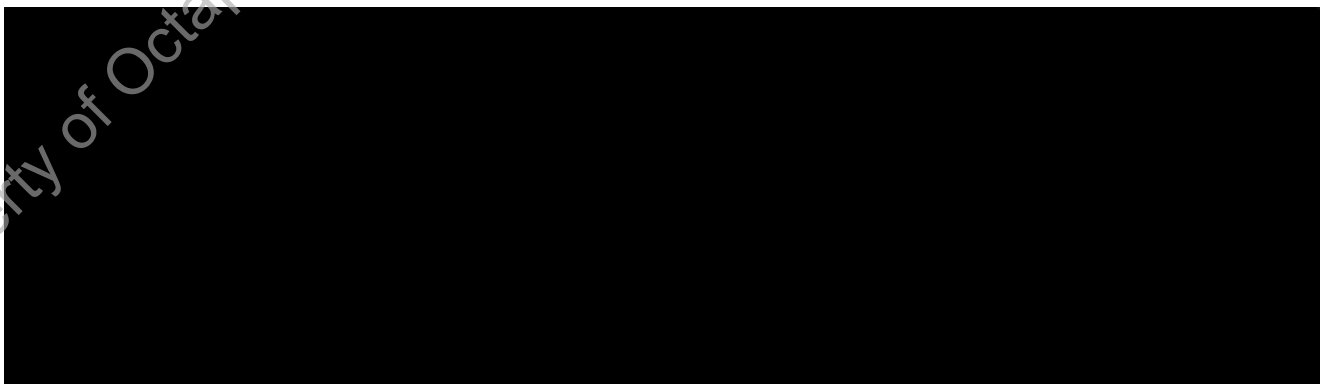


Table of Contents

1 SYNOPSIS

Name of Sponsor: Octapharma Canada	
Name of Investigational Products: *Wilate* and *Nuwiq*	**Study number:** WIL-26
Name of Active Ingredient: Human von Willebrand factor (VWF)/human coagulation factor VIII (FVIII) Recombinant factor VIII (rFVIII)	**Version / Date of Report:** 1.0 08-Oct-2021

Title of Study: Immune Tolerance Induction in Hemophilia A Patients using Wilate® or Nuwiq® – A Canadian Study (WIL-26)
Indication: Hemophilia A with inhibitor
Number of Study Centre(s): 2
Study Period First Patient In: 19-Jun-2018 Last Patient Out: 12-May-2020
Rationale and Background: Development of factor VIII (FVIII) inhibitors is the main complication in the treatment of patients with hemophilia A. Ideally, patients with hemophilia A should receive continuous, long-term prophylaxis to prevent joint and muscle bleeding and hemophilic arthropathy. However, prophylaxis with FVIII in patients with inhibitors is ineffective until there has been complete and sustained elimination of the inhibitor, defined as (1) no detectable inhibitor on at least 2 consecutive occasions, (2) normal in vivo recovery (IVR) and half-life, and (3) no reappearance of inhibitors during regular FVIII replacement. Immune tolerance induction (ITI) is a therapy intended to eradicate such inhibitors. High-dose FVIII treatment has been shown to effectively induce immune tolerance and to exert a long-lasting effect in more than 80% of treated patients. Success rates may vary, depending both on patient variables and on factors related to the therapeutic regimen, as well as on the product chosen for ITI including concentrate purity and von Willebrand factor (VWF) content. ITI with *Wilate* or *Nuwiq* has been shown to be a safe and effective treatment approach in a high-risk, adult patients with severe hemophilia A.

Name of Sponsor: Octapharma Canada	
Name of Investigational Products: *Wilate* and *Nuwiq*	**Study number:** WIL-26
Name of Active Ingredient: Human von Willebrand factor (VWF)/human coagulation factor VIII (FVIII) Recombinant factor VIII (rFVIII)	**Version / Date of Report:** 1.0 08-Oct-2021

As the current study was underway, a larger, global multicentre Phase 4 investigator-initiated study with a similar study objective, design and outcomes was launched. Given the similarities between the two studies, although the goal was to recruit 80 Canadian patients into the current study, it was decided that being a part of a larger study would both accelerate patient recruitment and address the clinical question with more robustness. Therefore, the investigators decided to stop the study and encourage all participating study sites to enrol eligible patients into the new international study.

Objectives:

Primary Objective:

The primary objective of this study was to evaluate the efficacy of *Wilate* or *Nuwiq* in achieving complete or partial ITI success in severe, moderate and mild hemophilia A patients with inhibitors.

Secondary Objectives:

The secondary objectives of this study were to:

- Evaluate the time to achieve immune tolerance to FVIII with ITI treatment using *Wilate* or *Nuwiq*,
- Evaluate the bleeding frequency while on *Wilate* or *Nuwiq* ITI treatment,
- Evaluate the relapse rate and time to relapse following successful ITI using *Wilate* or *Nuwiq*.

Additional Objectives:

The additional objectives of this study were to record the patients' general and hemophilia-specific quality of life, inhibitor biology (i.e., epitope mapping, IgG subclasses, antibody binding affinity), thrombin generation assay (TGA), and genotyping.

Study Design:

Uncontrolled, multi-centre, non-interventional study with a prospective and a retrospective cohort

Name of Sponsor: Octapharma Canada	
Name of Investigational Products: *Wilate* and *Nuwiq*	**Study number:** WIL-26
Name of Active Ingredient: Human von Willebrand factor (VWF)/human coagulation factor VIII (FVIII) Recombinant factor VIII (rFVIII)	**Version / Date of Report:** 1.0 08-Oct-2021

Subjects and Study Size, Including Dropouts:

It was planned that a total of at least 80 patients will be enrolled into this study, i.e., at least 40 evaluable hemophilia A patients with an inhibitor against FVIII into the prospective cohort and a maximum of 40 evaluable hemophilia A patients with an inhibitor against FVIII into the retrospective cohort. At the time of study termination, 14 patients had been enrolled.

Patient Selection Criteria:

Inclusion Criteria:

1. Male patients of any age with mild, moderate or severe hemophilia A.
2. Patients with a first occurrence of inhibitors, inhibitors refractory to previous ITI attempt(s), or relapsed inhibitors to FVIII, with an inhibitor titre of ≥0.6 Bethesda Units (BU) measured on 2 separate occasions at least 2 weeks apart.
3. Informed written consent from the patient and/or the patient's parent(s) or legal guardian(s).

For patients included in the prospective cohort:

4. Patients who were currently on *Wilate* or *Nuwiq* ITI, had just initiated ITI, or were planned to initiate ITI treatment with *Wilate* or *Nuwiq*.

For patients included in the retrospective cohort:

4. Patients having received *Wilate* or *Nuwiq* for ITI before entry into this study. Retrospective data was to be collected for a maximum of 3 years prior to enrolment into the study. To be eligible, the following information was needed for the time period while on ITI therapy:
   - *Wilate* or *Nuwiq* treatment details (start date, dose, treatment frequency, and dose change)
   - Reliably documented bleeding frequency
   - FVIII inhibitor titres
   - FVIII half-life
   - FVIII IVR

Name of Sponsor: Octapharma Canada	
Name of Investigational Products: *Wilate* and *Nuwiq*	**Study number:** WIL-26
Name of Active Ingredient: Human von Willebrand factor (VWF)/human coagulation factor VIII (FVIII) Recombinant factor VIII (rFVIII)	**Version / Date of Report:** 1.0 08-Oct-2021

Exclusion Criteria:

1. Congenital or acquired bleeding disorders other than hemophilia A.
2. A history of hypersensitivity to blood products and/or plasma-derived FVIII concentrates.
3. Inability to speak/read English or French well enough to provide consent and adhere to the study.
4. Receiving other non-factor therapies, e.g., concizumab.

Test Product, Dose, Mode of Administration, and Batch Number(s):

Although it was planned to enroll patients treated with either *Wilate* or *Nuwiq*, all of the enrolled patients ended up being treated with *Wilate*, and no patient received *Nuwiq.*

Wilate was administered as an intravenous infusion.

The batches used were:

K634A1811, K634C1811, K617A1813, K617A1814, A550A1811, K637D1811, K642C1812, K646B1811, and K74801891.

Reference Product, Dose, Mode of Administration, and Batch Number(s):

Not applicable.

Study Outcome Parameters (Primary and Secondary Endpoints):

The primary endpoint was the proportion of patients achieving complete or partial ITI success.

Secondary endpoints were:

- Time to achievement of complete or partial ITI success,
- Duration of immune tolerance (in case of complete or partial ITI success),
- Bleeding frequency while on *Wilate* or *Nuwiq* ITI treatment,
- Association of inhibitor titres at the start of and throughout ITI treatment,
- Use of bypassing agents before and during ITI treatment with *Wilate* or *Nuwiq,*
- Use of emicizumab (Hemlibra®),
- Frequency and timing of relapses,

Name of Sponsor: Octapharma Canada	
Name of Investigational Products: *Wilate* and *Nuwiq*	**Study number:** WIL-26
Name of Active Ingredient: Human von Willebrand factor (VWF)/human coagulation factor VIII (FVIII) Recombinant factor VIII (rFVIII)	**Version / Date of Report:** 1.0 08-Oct-2021

- Treatment adherence,
- Treatment safety.

Additional endpoints planned to be assessed in substudies were:

- The patients' general and hemophilia-specific quality of life,
- Inhibitor biology (i.e., epitope mapping, IgG subclasses, antibody binding affinity),
- TGA,
- Genotyping.

Summary of Study Procedures and Statistical Methods:

During the screening visit, the demographic and baseline data, including the patient's medical, bleeding, and ITI history, comorbidities, Hemophilia Joint Health Score (HJHS), and history of present illness including inhibitor titres were documented.

Patients received a study diary in which they documented all bleeding episodes, treatment details, adverse drug reactions (ADRs), central-line infections, and infections resulting in hospitalization. Follow-up visits were as per standard of care at each study site, with a recommended visit interval of at least 3 months.

No statistical analysis was performed on the data collected. Safety and efficacy data are presented descriptively.

Summary of Results & Discussion:

No new safety signals emerged in this study and the ADRs were those expected in a population of patients with hemophilia A. Five ADRs were judged as unlikely related and 1 not related to *Wilate*. There were no deaths during the study. Two patients experienced 3 serious ADRs (gastroenteritis, an infected implantable venous access device [IVAD], respiratory distress). All ADRs resolved.

Efficacy evaluation results were available for 8 of the 14 patients. For 7 patients, the treatment with *Wilate* was judged as 'complete success' and for 1 (12.5%) as 'complete failure', giving the success rate of 87.5%.

Wilate ITI was well tolerated in this group of paediatric previously treated patients with hemophilia A and no new safety concerns were raised.

2 LIST OF ABBREVIATIONS

ADR	Adverse drug reaction
BE	Bleeding episode
BU	Bethesda Units
FVIII	Coagulation factor VIII
HJHS	Hemophilia Joint Health Score
ITI	Immune tolerance induction
IVAD	Implantable venous access device
IVR	In vivo recovery
PP	Per-protocol (population)
rFVIIa	Recombinant activated factor VII
SD	Standard deviation
TGA	Thrombin generation assay
VWF	von Willebrand factor
VWF:Ag	von Willebrand factor antigen

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This was an uncontrolled, multi-centre non-interventional study with both a prospective and a retrospective cohort.

A total of at least 80 patients were planned to be enrolled into this study, i.e., at least 40 evaluable hemophilia A patients with an inhibitor against coagulation factor VIII (FVIII) into the prospective cohort and a maximum of 40 evaluable hemophilia A patients with inhibitors against FVIII into the retrospective cohort. Each patient was to be followed for a maximum time period of 5 years after the start of *Wilate* or *Nuwiq* immune tolerance induction (ITI) therapy. The study was planned to be conducted in a maximum of 15 hemophilia treatment centres throughout Canada. The overall study duration was planned to be 10 years (Q2 2017 to Q4 2026).

Based on the decision of the treating physician in the participating centre, male patients of any age with mild, moderate (1% to 5% factor activity) or severe hemophilia A (<1% factor activity) with inhibitors to FVIII scheduled to undergo ITI treatment with *Wilate* or *Nuwiq* (prospective cohort) or having received *Wilate* or *Nuwiq* ITI in the 3 years before enrolment into the study (retrospective cohort) were to be included into this study. This study was also open for subjects who failed earlier ITI attempt(s).

The dose and frequency of ITI treatment were at the discretion of the treating physician. However, use of one of the treatment protocols described in the Protocol, Section 7.4.2 was recommended.

The primary endpoint was the proportion of patients achieving complete or partial ITI success. The criteria for the definition of ITI success are summarized in Table 1.

Table 1 Criteria for the Definition of Success of ITI

Complete success	1. Inhibitor titre <0.6 BU (at least 2 separate blood samplings) 2. Incremental IVR of FVIII in the normal range (≥66% of normal) 3. FVIII half-life ≥6 hours
Partial success	Two of the three criteria above were met.
Partial response	One of the three criteria above was met.
Partial failure	None of the three criteria were met, but inhibitor titre has decreased to <5 BU.
Complete failure	None of the three criteria were met, and inhibitor titre was still ≥5 BU.

BU, Bethesda Unit; FVIII, coagulation factor VIII; ITI, immune tolerance induction; IVR, in vivo recovery.

Secondary endpoints included the time to achievement of complete or partial ITI success, the duration of immune tolerance (in case of complete or partial ITI success), bleeding frequency while on *Wilate* or *Nuwiq* ITI treatment, association of inhibitor titres at the start of and throughout ITI treatment with the probability of ITI success, use of bypassing agents before and during ITI treatment with *Wilate* or *Nuwiq*, the use of emicizumab (Hemlibra®), the frequency and timing of relapses, treatment adherence, and treatment safety. Additional endpoints planned to be assessed in substudies were the patients' general and hemophilia-specific quality of life, inhibitor biology (i.e., epitope mapping, IgG subclasses, antibody binding affinity), thrombin generation assay (TGA), and genotyping.

An overview of the time points and assessments at screening/study visits is provided in Table 2 and Table 3 below.

Briefly, during the screening visit, the demographic and baseline data, including the patient's medical, bleeding, and ITI history, comorbidities, Hemophilia Joint Health Score (HJHS), and history of present illness including inhibitor titres were documented.

Patients received a study diary in which they documented all bleeding episodes (BEs), treatment details, adverse drug reactions (ADRs), central-line infections, and infections resulting in hospitalization. Follow-up visits were as per standard of care at each study site, with a recommended visit interval of at least 3 months.

Table 2 Recommended Flow Chart of Assessments for Patients in the Prospective Cohort

	Parameter		Screening	Pre-treatment	Immune tolerance therapy (ITI)			End of ITI	ITI follow-up (every 12 months until month 60)
					0–3 months	3–6 months	6–36 months (c)		
	Demographic and baseline information		x						
	Hemophilia Joint Health Score (HJHS)		x			every 6 months		x	x
	General condition		x	x	x	x	x	x	x
	Inhibitor titre and FVIII trough levels		x	x	twice monthly, at least monthly	monthly	3-monthly	x	approx. every 3 months
	VWF:Ag trough levels		x		1 month after ITI start				
	VWF:Ag peak levels				1 month after ITI start (j)				
	FVIII IVR				(a)	(a)	(a)	x	x
	FVIII half-life				(a) and (b)	(a) and (b)	(a) and (b)	x	
	ITI efficacy assessment							x	
Substudies	**Quality of life**	**High-titre inhibitor patients**		x	3 months after ITI start	(d)	(d)	x	(e)
		Low-titre inhibitor patients		x	3 months after ITI start			x	(e)
	Anti-FVIII antibody characterization studies (f)		x (k)		every 12 months (i) (k)				
	Thrombin generation assay (TGA)								
	Genotyping		At any time during ITI						
	Recording of ITI treatment regimen		Continuously						
	Documentation of bleeding episodes (g)		Continuously						
	Documentation of surgeries (g)		Continuously						
	ADRs and infections (h)		Continuously						
	Concomitant medications (l)		Continuously						

(a) when Bethesda negative (<0.6 BU); (b) if recovery ≥66% of expected; (c) if applicable; (d) when patient had reached <5 BU; (e) after 12, 24, 36, 48, and 60 months; (f) included epitope mapping, determination of IgG subclasses, and assessment of antibody binding affinity (g) including treatment efficacy assessments; (h) Infections of special interest were defined as central-line infections and infections leading to hospitalization (i) as long as inhibitor levels were measurable using the Bethesda assay; (j) samples should have been taken 1 hour after infusion of *Wilate*; (k) blood sample for TGA assessment was to be taken 1 hour after infusion; (l) Concomitant medications included bypassing agents, vaccinations, and immunomodulating therapies.

Table 3 Recommended Flow Chart of Assessments for Patients in the Retrospective Cohort

	Parameter	Screening	Pre-treatment	Immune tolerance therapy (ITI)			End of ITI	ITI follow-up (every 12 months until month 60)
				0–3 months	3–6 months	6–36 months (c)		
	Demographic and baseline information	x						
	Hemophilia Joint Health Score (HJHS)	Available data should be documented						
	General condition	x	x	x	x	x	x	x
	Inhibitor titre and FVIII trough levels	Available data should be documented						
	VWF:Ag trough levels							
	VWF:Ag peak levels							
	FVIII IVR							
	FVIII half-life							
	ITI efficacy assessment						x	
Substudies	Anti-FVIII antibody characterization studies (a)	NA, but in case any retention samples are available, these can be provided for testing						
Substudies	Thrombin generation assay (TGA)							
Substudies	Genotyping	At any time during the study						
	Recording of ITI treatment regimen	Continuously						
	Documentation of bleeding episodes (b)	Continuously						
	Documentation of surgeries (b)	Continuously						
	ADRs and infections (c)	Continuously						
	Concomitant medications (d)	Continuously						

(a) included epitope mapping, determination of IgG subclasses, and assessment of antibody binding affinity (b) including treatment efficacy assessments; (c) Infections of special interest were defined as central-line infections and infections leading to hospitalization; (d) Concomitant medications included bypassing agents, vaccinations, and immunomodulating therapies.

4 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

The current study was conceived as a Canadian study to evaluate the safety and efficacy of ITI in hemophilia A patients using either *Wilate* or *Nuwiq*. However, all of the enrolled patients ended up being treated with *Wilate*, and no patient received *Nuwiq*. Additionally, with the introduction of non-factor treatments as an option to treat hemophilia A patients with inhibitors to FVIIII, alone or in combination with emicizumab, the investigators amended the protocol to include emicizumab to the treatment protocol. At the same time, a larger, global multicentre Phase 4 investigator-initiated study with a similar study objective, design and outcomes was launched (MOTIVATE). Given the similarities between the two studies, although the goal was to recruit 80 Canadian patients into the current study, it was decided that being a part of a larger study would both accelerate patient recruitment and address the clinical question with more robustness. Therefore, the investigators decided to stop the study and encourage all participating study sites to enrol eligible patients into the new international study.

5 RESULTS

5.1 Disposition of Patients

A total of 14 patients were enrolled in this study, 8 in the retrospective and 6 in the prospective cohort. All patients were treated with *Wilate*. Two patients, both from the retrospective cohort, were excluded from the per-protocol (PP) population: one (26-01-02) switched to an alternative treatment and the other (26-01-07) experienced better response with recombinant activated factor VII (rFVIIa) (OCTA-WIL26_DM_Export, OCTA-WIL26_DS_Export). No patient discontinued the study before it was terminated.

5.2 Patient Demographics

Patient demographics and baseline characteristics are summarized in Table 4. Inhibitor levels prior to entering the study are shown in OCTA-WIL26_MHI_Export.

Table 4. Baseline Characteristics

	Number of Patients N=14
Age (years)	
n	14
Mean (SD)	12.4 (6.1)
Median	11.0
Range	(4–23)
Race, n (%)	
n	14
Asian	1 (7.1)
White	9 (64.3)
Other[1]	3 (21.4)
Missing	1 (7.1)
Blood type, n (%)	
n	14
0	5 (35.7)
A	4 (28.6)
B	1 (7.1)
AB	3 (21.4)
Missing	1 (7.1)
Severity of hemophilia A, n (%)	
n	13
Mild	7 (50)
Moderate (1% to 5% factor activity)	2 (14.3)
Severe (<1% factor activity)	4 (28.6)
Missing	1 (7.1%)
FVIII mutation, n (%)	
n	13
Intron 22 Inversion	6 (42.9)
Intron 1 Inversion	1 (7.1)
Missense mutations	1 (7.1)
Unknown	5 (35.7)
Missing	1 (7.1)
Previous inhibitor treatment, n (%)	
n	14
Yes	10 (71.4)
No	4 (28.6)

1. Other includes: Asian/White n=1, Indian/White n=1, Middle-Eastern n=1.
SD, standard deviation.
Source: OCTA-WIL26_DM_Export, OCTA-WIL26_DH_Export, OCTA-WIL26_CMP_Export.

5.3 Safety Evaluation

5.3.1 Extent of Exposure

Available data on the exposure to *Wilate* is provided in OCTA-WIL26_EX_Export, OCTA-WIL26_EXHL_Export and OCTA-WIL26_EXOP_Export.

5.3.2 ADRs and Infections

5.3.2.1 Brief Summary of ADRs

Of the 14 patients, 2 experienced 6 ADRs in the study (patient 26-01-02 experienced 4 ADRs and patient 26-01-08 experienced 2 ADRs) (Table 5).

Table 5: Summary Statistics on Patients with ADRs (Safety Population, N=14)

	All patients n (%)	Number of ADRs
ADR	2 (14.3)	6
Serious ADR	2 (14.3)	3
Related ADR[1]	0	0
Serious related ADR	0	0
Severe ADR[2]	2 (14.3)	4
ADR leading to discontinuation of study medication	0	0
Related ADR leading to discontinuation of study medication	0	0
ADR leading to death	0	0

1. Five ADRs were judged as "unlikely" related and one as "not related".
2. Severity of one ADR was not rated.

ADR, adverse drug reaction.
Source: OCTA-WIL26_AE_Export.

Of the 6 ADRs, 4 (66.7%) were severe, 1 (16.7%) was of moderate severity and for 1 the severity was not recorded. Three (50%) of the ADRs were judged as serious. Three (2 serious) ADRs were of special interest. Serious ADRs and those of special interest are discussed in Section 5.3.2.3. All ADRs resolved and all patients recovered from the ADRs. Five of the ADRs were judged as unlikely related to the study drug and one was judged as not related. There were no deaths in the study (OCTA-WIL26_AE_Export).

5.3.2.2 Display of Adverse Drug Reactions

The list of ADRs recorded is shown in Table 6.

Table 6: Display of ADRs by MedDRA Preferred Term (Safety Population, N=14)

ADR	Number of patients (%)	Number of ADRs
Any ADR	**2 (14.3)**	**6**
Device-related infection	1 (7.1)	2
Gastroenteritis	1 (7.1)	1
Bronchial hyperreactivity	1 (7.1)	1
Respiratory distress	1 (7.1)	1
Pyrexia	1 (7.1)	1

ADR, adverse drug reaction; IVAD, implantable venous access device.
Source: OCTA-WIL26_AE_Export.

5.3.2.3 Analysis of ADRs and Infections

All ADRs were single occurrences, with 4 ADRs in one and 2 ADRs in another patient.

A 5-year-old White patient (26-01-02) experienced 4 ADRs in the study. This patient was admitted for implantable venous access device (IVAD) line infection on 19-Mar-2014. This event was judged as severe. The patient underwent a removal of the IVAD on 20-Mar-2014 (planned procedure, major surgery). On 26-Mar-2014, he experienced gastroenteritis of moderate severity and judged as a serious ADR, and the next day (27-Mar-2014), exacerbation of airway reactive disease, which was judged as severe. He underwent an insertion of a 6-French petite port-a-cath at the right subclavian vein on 27-Mar-2014 and a port-a-cath revision on 11-May-2014 (both major surgeries). All 3 ADRs resolved by 03-Apr-2014. The ADRs were judged as unlikely related to the treatment. On 01-Jan-2015, this patient had an infected IVAD (ADR judged as severe and serious), which was removed the next day (02-Jan-2015; major surgery), and the ADR resolved by 04-Jan-2015. He additionally underwent an insertion of IVAD via left subclavian vein on 13-Jan-2015 (OCTA-WIL26_AE_Export, OCTA-WIL26_OP_Export).

A 17-month-old patient of Indian descent (26-01-08) experienced respiratory distress, judged as severe and serious and not related to the study treatment, on 12-May-2019. The ADR resolved on 17-May-2019. This patient also reported fever on 13-Sep-2019, which resolved the same day. The severity of this ADR was not reported. The event was judged as unlikely related to *Wilate*. The medical history of this patient shows that he was born prematurely at 35 weeks, and exhibited a failure to thrive in the first week of life. He was diagnosed with tracheoesophageal fistula with esophageal atresia at birth. During the study, he underwent multiple procedures (7 esophageal dilations, 3 bronchoscopies and 3 laryngoscopies, 4 esophagogastroduodenoscopies) as a result of this condition (OCTA-WIL26_AE_Export, OCTA-WIL26_MH_Export, OCTA-WIL26_OP_Export).

The 2 IVAD line infections and the gastroenteritis in one patient were judged as ADR of special interest (infections).

5.3.2.4 Listing of Adverse Events by Patient

A complete list of ADRs by patient is given in OCTA-WIL26_AE_Export.

5.3.3 Deaths, Other Serious ADRs, and Other Significant ADRs

5.3.3.1 Listing of Deaths, other Serious ADRs and Other Significant ADRs

There were no deaths in this study (OCTA-WIL26_AE_Export). Serious ADRs and ADRs of special interest are described in Section 5.3.2.3.

5.3.3.2 Deaths

Not applicable.

5.3.3.3 Other Serious ADRs

The 3 serious ADRs are described in Section 5.3.2.3.

5.3.3.4 Other Significant ADRs

The 3 ADRs of special interest are described in Section 5.3.2.3.

5.3.3.5 Narratives of Deaths, Other Serious ADRs and Certain Other Significant ADRs

The 3 serious ADRs are described in Section 5.3.2.3.

5.3.3.6 Analysis and Discussion of Deaths, Other Serious ADRs and Other Significant ADRs

The 3 serious ADRs are described in Section 5.3.2.3.

5.3.4 Clinical Laboratory Evaluation

5.3.4.1 Listing of Individual Laboratory Measurements by Patient and Each Abnormal Laboratory Value

Individual patient data for hematology and biochemistry parameters during surgeries can be found in OCTA-WIL26_LBO_Export. Individual patient data for FVIII levels during surgeries can be found in OCTA-WIL26_OPLB_Export.

5.3.4.2 Evaluation of Each Laboratory Parameter

The following laboratory parameters examined included: hemoglobin, hematocrit, platelets, white blood cell count, alanine amino transferase, aspartate transaminase, serum creatinine and red blood cell count (OCTA-WIL26_LBO_Export).

5.3.4.3 Individual Clinically Significant Abnormalities

There were no laboratory values during surgeries judged as clinically significant (OCTA-WIL26_LBO_Export).

5.3.4.4 FVIII Inhibitors

Individual patient data for FVIII inhibitors can be found in OCTA-WIL26_LBIFV_Export.

5.3.5 Vital Signs, Physical Findings and Other Observations Related to Safety

Vital signs were not recorded.

5.3.6 Safety Conclusions

There were no deaths during the study. Two patients experienced 3 serious ADRs (gastroenteritis and infected IVAD in one and respiratory distress in the other). Gastroenteritis and infected IVAD were judged as unlikely related to *Wilate* and respiratory distress as not related to *Wilate*. All ADRs resolved.

Wilate ITI was well tolerated in this group of paediatric previously treated patients with hemophilia A and no new safety concerns were identified.

5.4 Analysis of Efficacy

The primary objective of this study was to evaluate the efficacy of *Wilate or Nuwiq* in ITI in moderate and severe hemophilia A patients with FVIII inhibitors by determining the proportion of patients achieving complete or partial ITI success based on predefined success criteria (Table 1).

Efficacy evaluation was performed for 8 of the 14 patients. For 7 patients (87.5%), the treatment with *Wilate* was judged as ‘complete success’ and for 1 (12.5%) as ‘complete failure’ (OCTA-WIL26_EA_Export). The patient for whom the treatment was judged as a failure (26-01-07) had a low-level inhibitor (2.5 Bethesda Units [BU]) at the start of ITI (22-May-2012). By 25-Jun-2012, his inhibitor levels were undetectable. Over the next 2 years, he had 2 more instances of low-level inhibitor, with other tests being negative for inhibitor activity. On 06-Oct-2014, he had a level of 0.8 BU, and at the next time point of 3.1 BU. On 19-Nov-2015 his inhibitor level was 209.0 BU and his ITI treatment declared as failed. The in

vivo recovery (IVR) values for this patient were not available. The patient was treated with 1500 IU (92.6 IU/kg) *Wilate* daily from 07-Jun-2012 until 12-May-2014, at which point the dose was increased to 2000 IU (109.9 IU/kg) daily and he continued this treatment until 04-Nov-2014. The dose was then increased to 3000 IU (152.3 IU/kg) daily, which he received until the end of ITI treatment. He experienced 8 bleeding episodes during the study (3 due to trauma, 1 spontaneous and 4 due to unknown causes). Five of the BEs were in an ankle, 1 one was a bilateral forearm muscle bleed, 1 was in his foot and 1 in his wrist. Five were moderate to major bleeds (3 ankle, 1 bilateral forearm and 1 wrist BE) and the severity for the other bleeds was not specified (OCTA-WIL26_LBIFV_Export, OCTA-WIL26_LBFR_Export, OCTA-WIL26_EX_Export, OCTA-WIL26_BE_Export).

5.5 Discussion and Overall Conclusions

The primary endpoint of this study was to evaluate the efficacy of *Wilate* or *Nuwiq* in achieving complete or partial ITI success in severe, moderate and mild hemophilia A patients with inhibitors. Due to the study termination, only 14 patients are included in this analysis. All patients were treated with *Wilate*.

Efficacy evaluation results were available for 8 of the 14 patients. For 7 patients, the treatment with *Wilate* was judged as ‘complete success’ and for 1 (12.5%) as ‘complete failure’, giving the success rate of 87.5%.

No new safety signals emerged in this study. There were no deaths during the study. Two patients experienced 3 serious ADRs (gastroenteritis and an infected IVAD in one and respiratory distress in the other). Gastroenteritis and infected IVAD were judged as unlikely related to *Wilate* and respiratory distress as not related. All ADRs resolved.

Wilate ITI was well tolerated in this group of paediatric previously treated patients with hemophilia A and no new safety concerns were raised. Therefore, these results are in line with those reported for other studies with *Wilate* ITI treatment in Canadian patients

6 TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

See Section 7.4.

7 APPENDICES

7.1 Protocol and Protocol Amendments

7.2 Sample Case Report Forms (Unique Pages Only)

7.3 Case Report Forms for Deaths, Other Serious Adverse Events and Withdrawals for Adverse Events

7.4 Patient Data Listings

OCTA-WIL26-AE-Export

OCTA-WIL26-BE-Export

OCTA-WIL26-BEP-Export

OCTA-WIL26-CM-Export

OCTA-WIL26-CMHT-Export

OCTA-WIL26-CMP-Export

OCTA-WIL26-CO-Export

OCTA-WIL26-DH-Export

OCTA-WIL26-DM-Export

OCTA-WIL26-DS-Export

OCTA-WIL26-EA-Export

OCTA-WIL26-EX-Export

OCTA-WIL26-EXHL-Export

OCTA-WIL26-EXOP-Export

OCTA-WIL26-FA-Export

OCTA-WIL26-IE-Export

OCTA-WIL26-ITIP-Export

OCTA-WIL26-JS-Export

OCTA-WIL26-LBFR-Export

OCTA-WIL26-LBIFV-Export

OCTA-WIL26-LBO-Export

OCTA-WIL26-MH-Export

OCTA-WIL26-MHI-Export

OCTA-WIL26-MSW-Export

OCTA-WIL26-OP-Export

OCTA-WIL26-OPBL-Export

OCTA-WIL26-OPLB-Export

OCTA-WIL26-PE-Export

OCTA-WIL26-QOLA-Export

OCTA-WIL26-QOLC-Export
OCTA-WIL26-QOLHA-Export
OCTA-WIL26-QOLHK-Export
OCTA-WIL26-QOLI1-Export
OCTA-WIL26-QOLI2-Export
OCTA-WIL26-QOLT-Export
OCTA-WIL26-QOLTO-Export
OCTA-WIL26-QOLY-Export
OCTA-WIL26-RA-Export
OCTA-WIL26-REL-Export
OCTA-WIL26-SA-Export
OCTA-WIL26-SV-Export
OCTA-WIL26-VS-Export
OCTA-WIL26-WH-Export