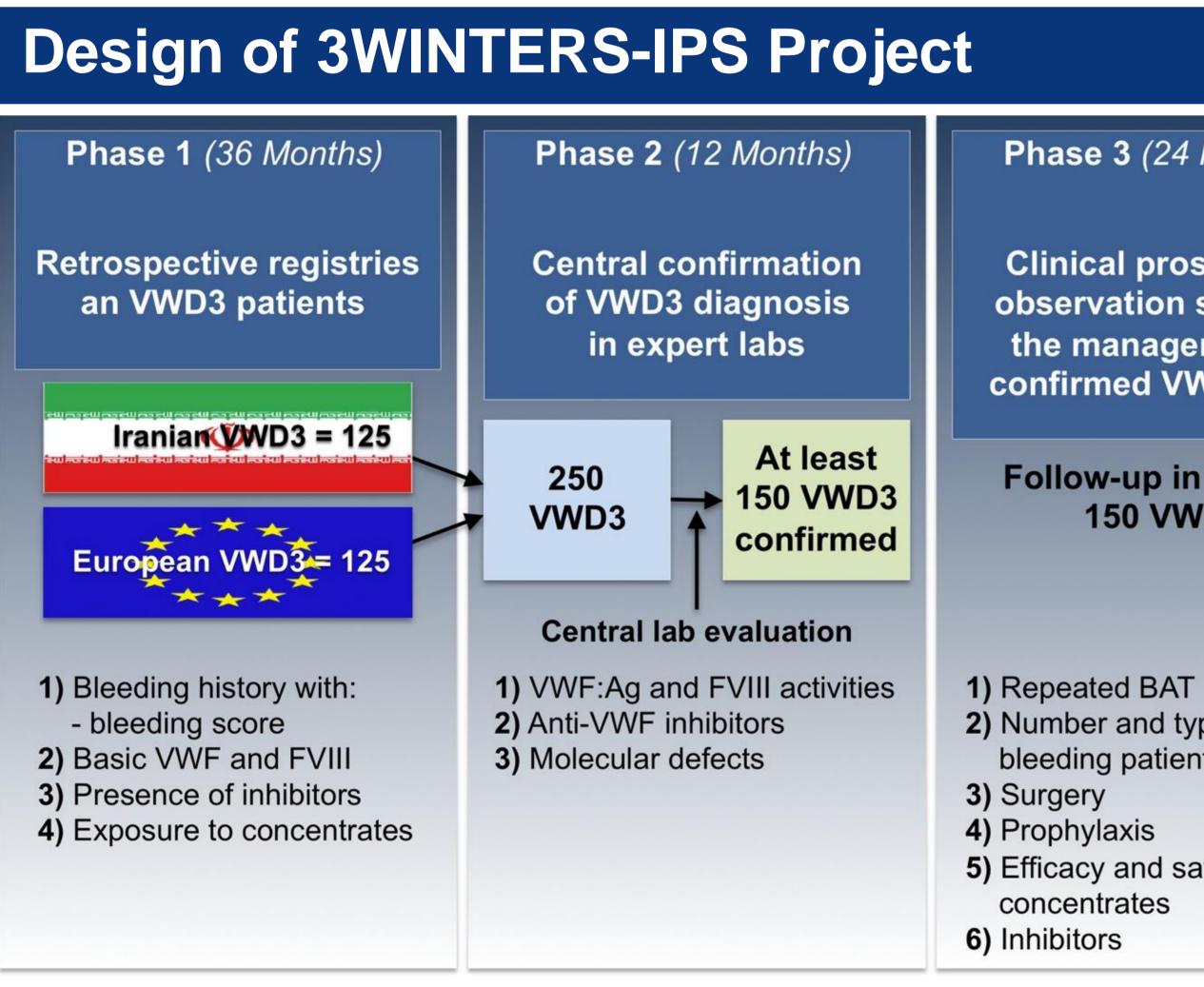
NEW INSIGHTS INTO TYPE 3 VON WILLEBRAND DISEASE: THE TYPE 3 VON WILLEBRAND DISEASE INTERNATIONAL REGISTRIES AND INHIBITOR PROSPECTIVE STUDY (3WINTERS-IPS) PROJECT UPDATE Augusto B Federici on behalf of 3Winters-Ips Investigators, Flora Peyvandi, Ulrich Budde, Giancarlo Castaman, Jeroen Eikenboom, Peyman Eshghi, Anne Goodeve, Jenny Goudemand, Hamid Hoorfar, Mehran Karimi, Ian R Peake, Reinhard Schneppenheim, Alberto Tosetto, Pier M Mannucci

Background

Von Willebrand disease type 3 (VWD3) is of major interest because of severe clinical presentation, need for replacement therapy with VWF/FVIII concentrates and the risk of anti-VWF inhibitors developing after treatment.

Aims

To evaluate in large cohort of VWD3 patients the relationship between standardised phenotypic, genotypic, clinical data and bleeding tendency, response to therapy with VWF/FVIII concentrates and the risk of anti-VWF inhibitor development.



Phase 1 of the Study (October 2011-October 2014) <u>2012</u> <u>2014</u> 1[/]2 15 18 21 2[/]4 27 30 October 31st, 2012 M1 October 31st, 2013 M2 **Milestones** October 31st, 2014 M3 M1 Implementation of network, database, website

<u>Tim</u>	<u>e schedule</u>	<u>Months</u>	0 :
<u>Wor</u>	<u>k Packages</u>		
WP1a	Network and Database	of the study	
WP1b	Ethical approval of the	Study	
WP2	Recruitment of VWD3 p	atients	
WP3	Bleeding history and ba	asic lab tests	

- Inclusion of at least 150 VWD3 patients
- Inclusion of all the 250 VWD3 patients

Phases 2 and 3 of the Study (October 2015-April 2018)

				<u>2015</u>				
<u>Time schedule</u>		Months 36	39	42	45	48		
<u>Work Packages</u>				1				
WP4a	Data and sample colle with distribution to cer							
WP4b	Confirmation laborator (VWF:Ag, FVIII, multim	•						
WP4c	Anti-VWF antibodies							
WP5	Mutation analysis in V	WD3						
WP6	Number type, risk fact in patients with confirm		osis					
WP7	Quantity, efficacy, safe different VWF concent	•						
WP8	Report on the use of V concentrates in VWD3							
			Octob	er 31 st	^t , 2015	M4		
<u>Milestones</u>								

- M4 Implementation into database of prospective CRF
- M5 Inclusion of confirmed VWD3 into prospective study (at least 150)
- M6 Report on VWD3 management with or without inhibitors

Methods

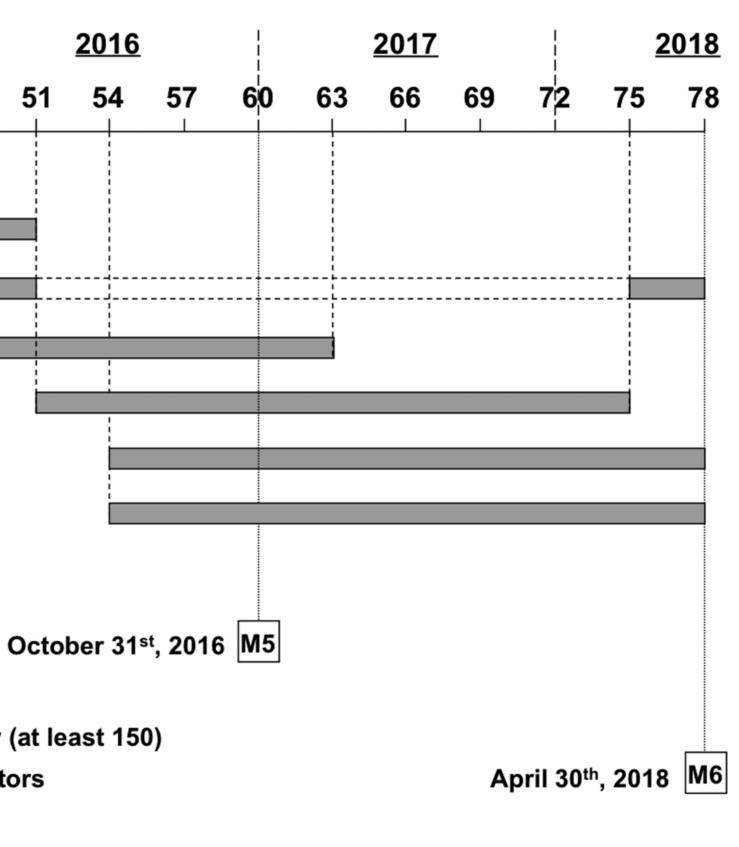
3WINTERS-IPS is a multicenter, European and observational, retrospective Iranian and with VWD3. prospective study on patients Patients meeting the enrolment criteria were enrolled at each participating centre and data entered into the project database.

Phase 3 (24 Months)

Clinical prospective observation study on the management in confirmed VWD3 only

Follow-up in at least 150 VWD3

2) Number and types of bleeding patients 5) Efficacy and safety of VWF



Results

251 VWD3 cases are included on the database with a gender distribution 106/145 (M/F); median age 27 (1-75) year and median bleeding score (BS) 12 (1-33). Median (range) of local lab test were: VWF:Ag 1.9 (<1-7) IU/dL; FVIII:C 2.3 (<1-15) IU/dL. Anti-VWF antibodies are reported present in 11. Molecular genetic analysis was undertaken at local sites in 55 patients all from EU sites. Of these, 31 (56%) are compound heterozygous (CH), 19 (35%) are homozygous (H) and 5 (9%) are apparently heterozygous with only one mutation found. In the CH group, there is a full range of mutation types including large deletions, small deletions/insertions, missense and nonsense mutations and splice site changes. One CH case had 2 missense mutations, both resulting in loss of a cysteine (p.C1227R and p.C2283R). Of the H group, 6 (31%) had splice and 5 (26%) had nonsense mutations. Of the 4 H with missense mutations, 2 resulted in loss of cysteines p.C2212R and p.C2362F and 2 had p.N2546Y. One H case had a gene conversion involving p.Q1311*.

Conclusions

VWD3 is This confirms initial data that phenotypically and genotypically heterogeneous.

Acknowledgements

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