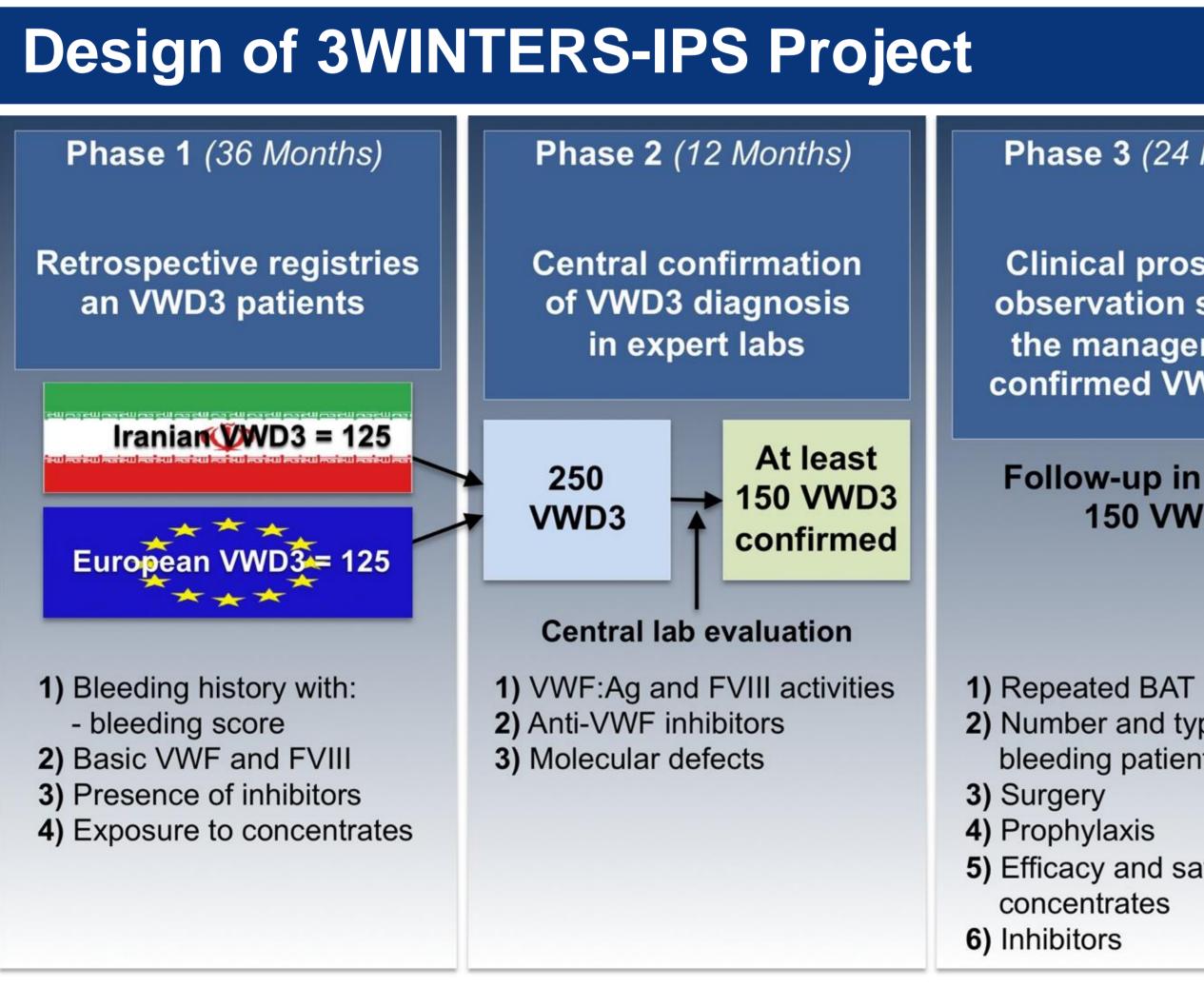
# NEW INSIGHTS INTO TYPE 3 VON WILLEBRAND DISEASE: THE TYPE 3 VON WILLEBRAND DISEASE INTERNATIONAL REGISTRIES AND INHIBITOR PROSPECTIVE STUDY (3WINTERS-IPS) PROJECT UPDATE Augusto B Federici on behalf of 3Winters-Ips Investigators, Flora Peyvandi, Ulrich Budde, Giancarlo Castaman, Jeroen Eikenboom, Peyman 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<sup>/</sup>2 15 18 21 2<sup>/</sup>4 27 30 October 31<sup>st</sup>, 2012 M1 October 31<sup>st</sup>, 2013 M2 **Milestones** October 31<sup>st</sup>, 2014 M3 M1 Implementation of network, database, website

<u>Tim</u>	<u>e schedule</u>	<u>Months</u>	<b>0</b> :
<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 <sup>st</sup>	<sup>t</sup> , 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

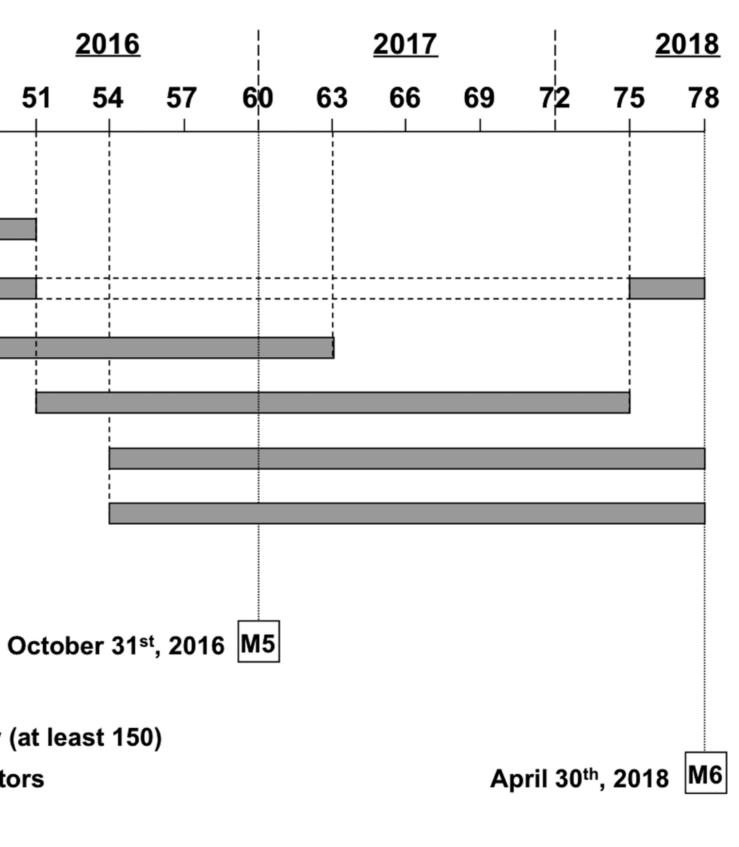
3WINTERS-IPS is a multicenter, European and observational, retrospective Iranian and with VWD3. prospective study on patients Patients meeting the enrolment criteria were enrolled at each participating centre and data entered into the project database.

### 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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