# NEW INSIGHTS INTO TYPE 3 VON WILLEBRAND DISEASE: THE TYPE 3 VON WILLEBRAND DISEASE INTERNATIONAL REGISTRIES AND INHIBITOR PROSPECTIVE STUDY (3WINTERS-IPS) PROJECT UPDATE

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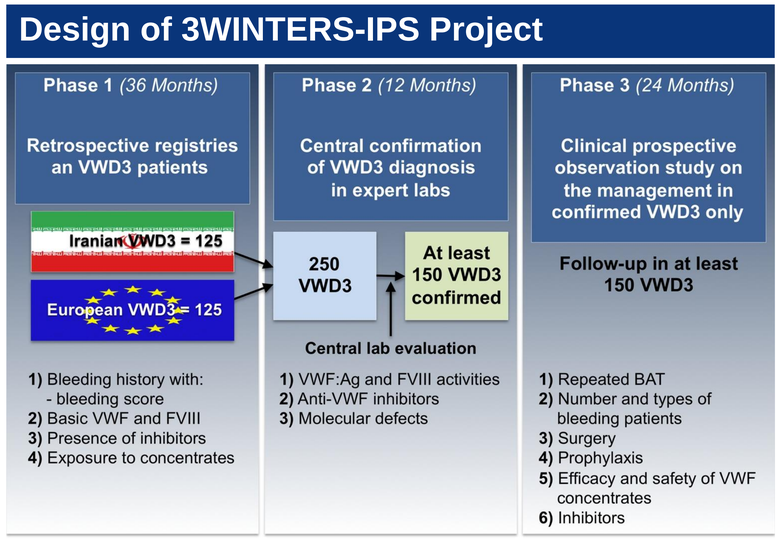
## Background

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.

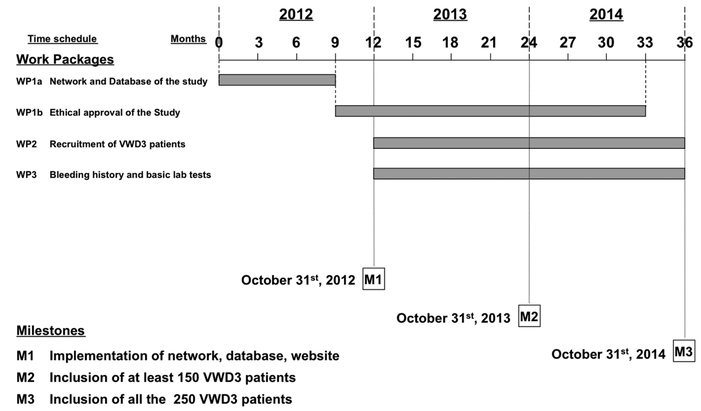
## Aims

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.

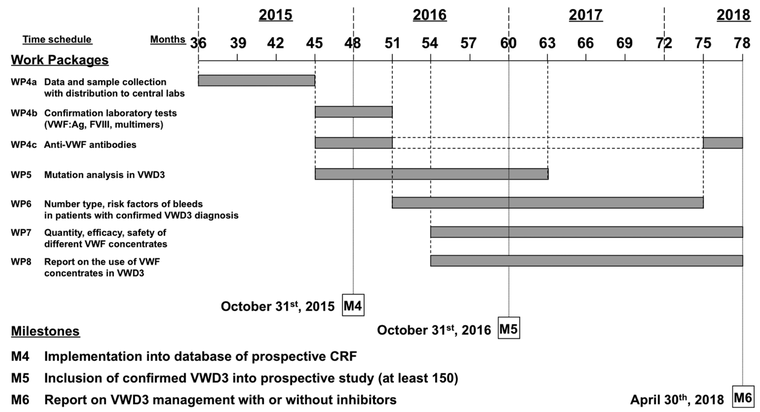
## Design of 3WINTERS-IPS Project




## Phase 1 of the Study *(October 2011-October 2014)*




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




## Methods

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

## 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

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

## Acknowledgements

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