ASP4021
NON-CONFIDENTIAL SUMMARY

astellas

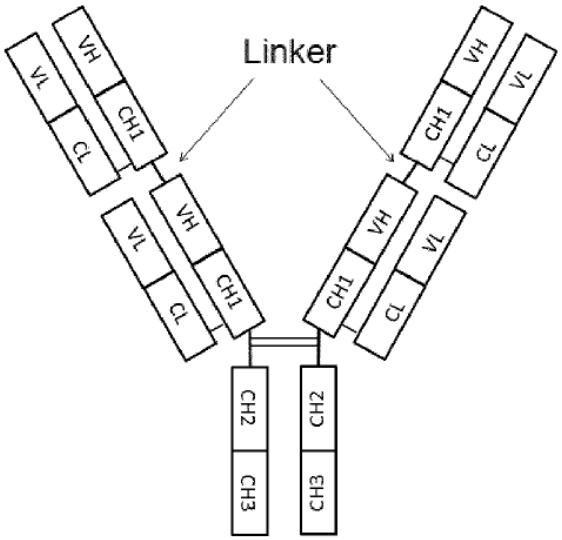
DISCLAIMER

This material includes forward-looking statements based on assumptions and beliefs in light of information currently available to the Astellas and subject to significant risks and uncertainties.

This material contains information on pharmaceuticals (including compounds in research or under development) and other matters. Notwithstanding the foregoing, Astellas makes no representations, warranties, assurances or guarantees of any kind or nature whatsoever, whether expressed or implied, regarding the information in the materials (including, without limitation, no representations, warranties, assurances or guarantees as to the accuracy, sufficiency or completeness of any information, as to whether Astellas has rights to any such information or pharmaceuticals/compounds, as to whether any third party has or does not have any rights to any of such information or pharmaceuticals/compounds, as to the safety, efficacy, or effectiveness of any preparations described in this material, as to the regulatory status of or potential for regulatory agency action regarding any pharmaceuticals/ compounds described in this material, or as to any uses, including unapproved uses, of any such preparations in any fashion). This material does not provide medical advice of any kind.

Astellas undertakes no obligation or duty to change, remove, add, clarify, correct or update any information in the materials at any time.

TETRAVALENT ANTI-HUMAN TIE2 ANTIBODY



Format of TIE-1-Igγ1-LALA

Binding Activity of TIE-1-Igγ1-LALA to Tie2

	EC_{50} value (ng/mL)			
	Human	Monkey	Rat	Mouse
TIE-1-Igγ1-LALA	0.565	0.545	0.633	0.696

Tie2 agonist activity* of TIE-1-Igγ1-LALA

	EC_{50} value	Maximum activity of anti-apoptotic activities
TIE-1-Igγ1-LALA	3.65 ng/mL	88%

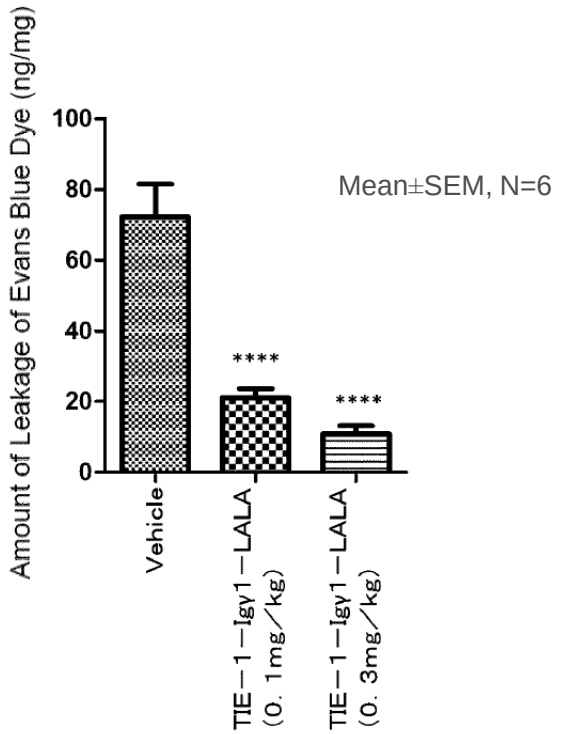
* anti-apoptotic activity using human Tie2-expressing BaF3 cell

WO 2016/010014A1

VASCULAR PERMEABILITY INHIBITORY ACTION OF TIE-1-IGΓ1-LALA IN A RAT MODEL WITH VASCULAR PERMEABILITY

Mustard oil-induced vascular permeability*

At 48 hours after the subcutaneous administration of TIE-1-Igγ1-LALA , an Evans Blue dye (45mg/kg) was intravenously administered, immediately 5% mustard oil was applied onto one ear, while the mineral oil was applied onto the contralateral ear.
After 30 minutes, both of the ears were sampled, weighed, then immersed in formamide to extract the Evans Blue dye in the ear tissue. The Evans Blue dye concentration was determined from the absorbance of the extract. Thereafter, by dividing the amount of the Evans Blue dye by the weight of the ear, the dye leakage amount per weight of the ear was calculated.



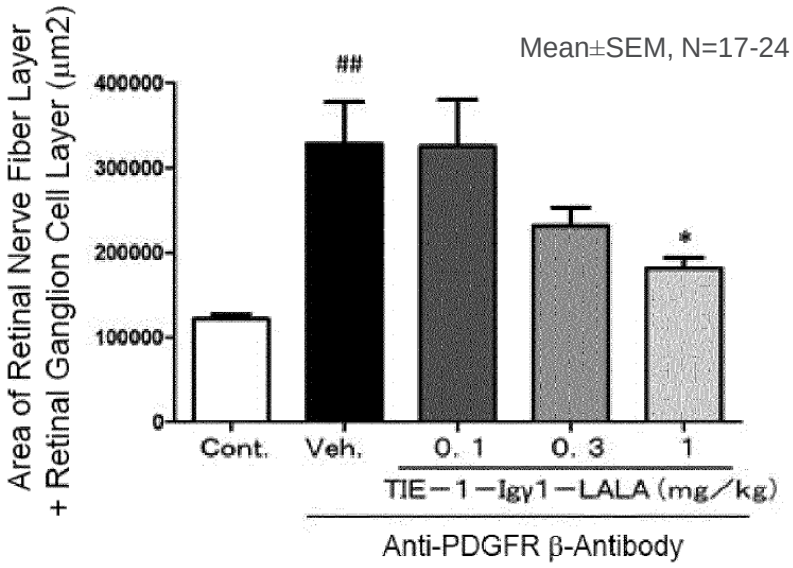
The vertical axis indicates the amount of leakage of an Evans Blue dye (****: p <0.0001 vs a vehicle group (Dunnett multiple comparison test).

*A mustard oil-induced vascular permeability model is a model with a modification applied to a Miles assay (J.Physiol., 1952, Vol. 118, pp. 228-257) which has been widely used as a plasma leakage evaluation system, and it has been reported that Ang-1 inhibits the vascular hyperpermeability in the present model (Nature Medicine, 2000, Vol. 6, pp. 460-463).

RETINAL EDEMA INHIBITORY ACTION OF TIE-1-IGΓ1-LALA IN A MOUSE MODEL WITH THE LOSS OF PERICYTES IN THE RETINAL BLOOD VESSEL

Pericyte loss-induced retinal edema*

At 90 minutes before administration of the anti-PDGFRβ antibody, TIE-1-Igγ1-LALA was subcutaneously administered.
At 1 week after administration of the antibody, retinal edema was evaluated. Specifically, the eyeball was extracted and fixed, and then a paraffin-embedded slice graft was prepared. In this model, retinal edema in the retinal nerve fiber layer (NFL) is reported, thereby quantification of retinal edema was carried out by measuring the areas of NFL and adjacent retinal ganglion cell layer.



The vertical axis indicates a sum of a retinal nerve fiber layer and a retinal ganglion cell layer (##: $p < 0.005$ vs Cont. group (Student t-test), *: $p < 0.05$ vs Veh. Group (Dunnett multiple comparison test).

*In the retinal blood vessels of a patient with diabetic retinopathy, the loss of pericytes is one of characteristic lesions (Retina, 2013, Fifth edition, pp. 925-939). In a mouse having the retinal blood vessels with the loss of pericytes by administration of an anti-PDGF receptor β (PDGFRβ) antibody, the lesions similar to those seen in diabetic retinopathy and diabetic macular edema, such as expansion of retinal blood vessel, retinal edema, and bleeding are observed, suggesting that the blood vessels are weakened like diabetic retinopathy and diabetic macular edema due to the loss of pericytes (J. Clin. Invest., 2002, Vol. 110, pp. 1619-1628).

CURRENT PROGRAM STATUS

- Pre-IND stage
- GLP-TOX studies (with systemic administration); Completed
- DS; No technical issues on CMC