ENCODE
IDEAS

TLC (Nasdaq: TLC, TWO: 4152)
INITIATION REPORT

April 27, 2020

Encode Ideas, L.P.
28 Rudnick Lane, Dover, DE 19901

FINANCIAL SUMMARY TABLE

Symbol	TLC
Exchange	NASDAQ
Current Price	$4.25*
52 week High	$8.54
52 week Low	$2.48
O/S	37.09mm**
Market Cap	~$157.6mm*
Average Volume (30D)	~2.2k
Cash	~$34.2mm**
Debt	~$10.4mm***

* as of 4/20/2020

** as of 12/31/2019

*** Cathay Bank loan balance as of 12/31/19

KEY CATALYST DATES

Q2 2020	Results from TLC590 Ph2 Study
Mid 2020	Results from TLC178 Ph1 Study
4Q 2020 (or Q1 2021)	Ph3 Initiation for TLC590
1H 2021	Full Enrolment in TLC599 Ph3 Study

KEY DISCLOSURES

One or more of the Encode Ideas, L.P. partners own stock in the covered company; Encode Ideas, L.P. is engaged with TLC to provide investor awareness and research coverage. Encode Ideas partners may continue transacting in TLC stock after the initiation of this report.

HIGH CONVICTION INVESTMENT IDEA

Encode Ideas is initiating on TLC as a high conviction investment idea. We believe TLC can achieve a market cap of ~400mm this year based on positive TLC590 Ph2 data, and growing investor enthusiam towards the completion of the TLC599 Ph3 study.

Taiwan Liposome Company (TLC) is a drug delivery/reformulation company with two late-stage assets focused on pain, and earlier stage assets for oncology and ophthalmology. Their most advanced asset, TLC599, an injectable liposomal formulation of the FDA-approved corticosteroid dexamethasone, is currently being evaluated in a pivotal Ph3 study for the treatment of osteoarthritis of the knee (knee OA). The company's most relevant peer, Flexion Therapeutics (Nasdaq: FLXN), has elevated medical and investor awareness around novel injectable corticosteroids formulations for knee OA with their approval and launch of ZILRETTA, which TLC stands to benefit from. We believe TLC599 addresses many of the shortcomings of Flexion's ZILRETTA, giving it best-in-class potential for the growing knee OA injectables market.

TLC's second pain asset, TLC590, a liposomal formulation of FDA-approved ropivacaine, is in development for postoperative pain. The company recently announced the completion of enrolment in a Ph2 bunionectomy study, and expects data this quarter. If successful, TLC would move to initiate a pivotal Ph3 program in 4Q20 / 1Q21, with studies in bunionectomy and hernia repair. Pacira Pharmaceuticals (Nasdaq: PCRX) is a highly relevant peer who developed a liposomal formulation of bupivacaine (branded as Exparel), a similar local analgesic to ropivacaine, into a successful commercial asset now approaching half a billion in annual sales. TLC is following a very similar development plan with TLC590 to that used by Pacira for its FDA-approval.

After its pain assets, TLC has two earlier stage assets, TLC399 and TLC178, focused on ophthalmology and oncology, respectively. We will not spend much time discussing these two earlier stage products, but highlight that TLC178, a liposomal formulation of FDA-approved chemotherapy vinorelbine, is currently being evaluated in a traditional 3+3 Ph1 dose escalation study, which should have data mid20. Data from this study will determine TLC's path forward for TLC178, which could include a Ph2/3 study in a rare cancer indication for paediatrics - rhabdomyosarcoma. It is worth noting that TLC's Founder and CEO, Keelung Hong, was co-inventor of Onivyde, a liposomal formulation of FDA-approved irinotecan, while at Hermes Biosciences. Onivyde's U.S. rights were eventually acquired by Ipsen for $575mm in 2017. So although earlier stage and not core to our investment thesis for TLC at this time, we note the pedigree in liposomal oncology drug development within the leadership team, and depending on the Ph1 outcome for TLC178, could foresee this asset's importance within the TLC pipeline increasing.

With an approximate $150mm market cap, we believe TLC is very affordable here. The company's Taiwanese roots including, listing on the Taipei Exchange listing (TWO: 4152), Taiwan based leadership, and Taiwanese investor base and finance history, all contribute to what we feel is a "foreign" discount applied to the valuation. This foreign discount coupled with the illiquidity of their Nasdaq listing, leads many investors to be dismissive of the opportunity, this is a mistake in our opinion. This pipeline is worth more than $150mm. We believe both TLC599 & 590 have excellent chances at clinical and eventually commercial success. We love the comparison between TLC599 and Flexion's ZILRETTA, and believe there is a compelling case for TLC599's superiority. TLC guided completion of enrolment in the pivotal Ph3 study would be in late 2020, but we are assuming a 3-6 month delay due to COVID-19. Therefore we are budgeting for completion of enrolment 1H21, and top-line data 1H22. In the meantime, TLC590 will have important Ph2 efficacy data in May/June that should not be impacted by COVID-19 and, if successful, should have a meaningful impact on TLC's valuation. We view TLC399 and TLC178 as call-options within the pipeline, but as highlighted above, could foresee a scenario where TLC178 becomes more prominent.

For those investors who are not deterred by illiquidity and can patiently build a position, we think a market cap of $400mm is achievable this year based on positive TLC590 Ph2 data and building enthusiasm around the completion of enrolment in the TLC599 Ph3 study. Looking further into the future, we believe a market cap >$1b is achievable based on Ph3 success with TLC599 in 2022 and anticipation for Ph3 data from TLC590.

HIGH CONVICTION INVESTMENT IDEA

TLC599 - The ZILRETTA Roadmap

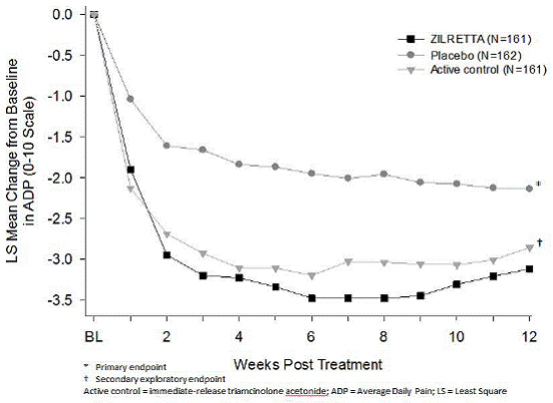
The dilemmas associated with the treatment of chronic inflammatory pain are well documented. In the case of knee OA, it is a progressive disease, that for some can eventually lead to complete knee arthroplasty (replacement). At its early stages, generic and OTC non-steroidal anti-inflammatory drugs (NSAIDs) can be effective, but their efficacy can become marginal as OA progresses. Furthermore long term chronic use of NSAIDs has been associated with serious GI and cardiovascular side effects. At the other end of the therapeutic spectrum are the opioids, unquestionably the best for pain management but with a high risk for abuse. Along the knee OA treatment paradigm, after NSAIDs but ideally before opioids, is the domain of the injectables. The U.S. injectables market includes platelet-rich plasma, viscosupplements (hyaluronic acid), immediate-release steroids, and one extended-release (ER) steroid, Flexion's ZILRETTA (triamcinolone acetonide). It is estimated that there are 8mm injections performed every year for knee OA in the U.S., and the vast majority, >80%, are steroid injections.

As the name implies, the benefit of an ER steroid is the duration of effect relative to their immediate release competitors. Flexion is the pioneer in the ER steroid market with its development of ZILRETTA. In the pivotal Ph3 knee OA study used for its approval, ZILRETTA demonstrated a statistically significant reduction in pain vs placebo at 12-weeks. Approved by FDA in late 2017 for the management of knee OA pain, ZILRETTA sales for FY19 were $73mm, and Flexion's revenue guidance for FY20 was $120-$135mm before rescinding due to the impact of COVID-19. Analyst estimates for peak annual ZILRETTA sales are between $500mm - $1b. Flexion has done an excellent job raising medical, and investor, awareness around the advantages of ER injectable steroid use, creating a great roadmap for TLC to follow.

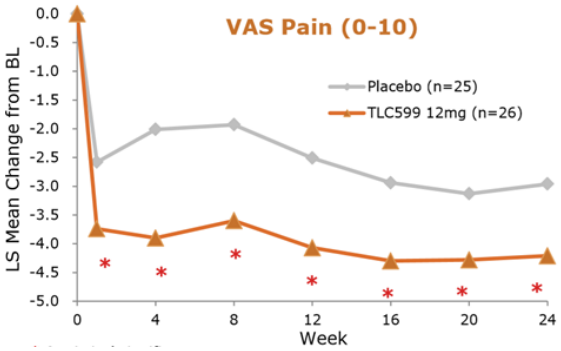
TLC599 - Best in Class Potential

TLC599, sustained-release dexamethasone sodium phosphate (DSP), is being evaluated in a multi-center, randomized, double-blind, placebo and active comparator (immediate release DSP) controlled pivotal Ph3 study, known as EXCELLENCE. The study is enrolling 500 patients with knee OA at a 2:1:1 randomization (TLC599 12mg: immediate release DSP: placebo). Study enrolment commenced in November 2019 and was originally expected to be completed late 2020, however, we think it appropriate to budget for a delay until 1H21. The study's primary endpoint is the change from baseline in pain for TLC599 vs placebo at Week 16 and Week 40. At week 24 patients can receive a second injection, for those patients in the immediate release DSP arm, their second injection will be TLC599.

The design of the Ph3 study is indicative of how TLC believes they can compete with the other injectables, most notably ZILRETTA, on duration of action and repeat use. In their earlier Ph2 knee OA study reported in 2018, TLC599 demonstrated a statistically significant reduction in pain scores starting at day 3 through week 24 vs placebo. These data are the impetus for TLC exploring longer duration of action in their primary pain endpoint, 16-week vs Zilretta's 12-week, in Ph3. Furthermore it is possible that if the Ph3 data replicate those in Ph2, and a statistically significant reduction in pain with TLC599 vs placebo still exists at 24-weeks, that a 6-month label from FDA is achievable. Regardless, we are encouraged to see TLC taking an aggressive approach towards differentiating TLC599 on duration of action vs the incumbent steroids, and think clinical success in Ph3 should translate to commercial success.



ZILRETTA Ph3 (above) vs. TLC599 Ph2 (below)



HIGH CONVICTION INVESTMENT IDEA

Expanding on the potential differentiation for TLC599, TLC is proactively exploring repeat dosing in Ph3. The predominant concern with repeat doses of injectable steroids is cartilage deterioration. In Ph2 TLC evaluated knee cartilage with MRI, and found that TLC599 was associated with less cartilage loss than control knees. As mentioned above, the ongoing Ph3 will evaluate the efficacy of repeat doses of TLC599 on pain reduction vs placebo. Success in Ph3 combined with the Ph2 imaging data, should make a compelling safety and efficacy argument for FDA to give TLC599 a repeat dose label. Flexion had been seeking an expanded label from FDA to allow repeat dosing of ZILRETTA. Earlier this year, FDA did allow a ZILRETTA label change (we are hesitant to use the word expansion in this case) from "ZILRETTA is not intended for repeat administration" to the rather curious language, "The efficacy and safety of repeat administration of ZILRETTA have not been demonstrated." This was heralded as a win by Flexion, but clearly FDA was uncomfortable giving a clean repeat dosing label for ZILRETTA. We believe repeat dosing is another area of potential differentiation for TLC599 vs ZILRETTA.

Looking further into the future, the blue-sky for TLC599 would include label expansion into other OA indications, likely shoulder and hip. Combined these indications are smaller than the knee OA opportunity, but they also could have less competition. TLC has greater flexibility with needle gauge size, due to the smaller volumes of DSP required as compared to TCA for ZILRETTA. We don't mean to "pile on" ZILRETTA, but Flexion recently had to discontinue their Ph3 study in hip OA due to "product administration issues", which we assume to be needle gauge related. Flexion continues to pursue shoulder OA, and is actively enrolling a Ph3 study. TLC hasn't discussed next steps for TLC599 beyond knee OA, but assuming they continue to follow the ZILRETTA roadmap, we can assume hip and shoulder OA are indications they will look to pursue.

TLC590 - The Exparel, or is it HTX-011, Roadmap

TLC590, a liposomal formulation of the anaesthetic ropivacaine, is being developed for postoperative pain management. Immediate release ropivacaine and bupivacaine are two of the more common local anaesthetics used for the management of postoperative pain (although we highlight that among the "caine" class that bupivacaine is substantially more popular for postoperative pain management).

Both immediate-release ropivacaine and bupivacaine are highly effective for postoperative pain management, but their duration of pain relief can be short-lived (<24-hr), leading to breakthrough pain, and the need for earlier and more frequent opioid use. In 2011 Pacira Pharmaceuticals received FDA approval for an ER liposomal formulation of bupivacaine, Exparel, for the management of postoperative pain. Since their initial FDA approval, Pacira has successfully expanded the Exparel label to include nerve block, but the majority of their sales, guided to be upwards of $500mm in 2020, are in the postoperative pain setting.

Much like Flexion created the clinical and commercial roadmap for ER steroids for knee OA, Pacira has done the same for ER local anaesthetics for postoperative pain with their development of Exparel. In general terms, the Exparel roadmap involves demonstrating a statistical difference in pain intensity vs placebo, measured by the Area Under the Curve score from 0 to 72 hours (AUC 0-72), in two surgical settings, bunionectomy and hernia repair. TLC is not the first to try and follow the Exparel development path, two notable and recent examples are DURECT Corp (Nasdaq: DRRX) and Heron Therapeutics (Nasdaq: HRTX), who both have ER bupivacaine formulations currently in front of FDA. Heron is particularly interesting to watch, as its product, HTX-011, has demonstrated statistical pain benefit (AUC 0-72) against both placebo and standard of care (SoC), immediate-release bupivacaine. Arguably Heron has raised the efficacy bar for what other ER local anaesthetics need to demonstrate in their pivotal programs by showing superiority for HTX-011 versus SoC.

TLC590 - Facing Bupivacaine Head-On

Much like its development of TLC599, TLC is facing its current and future competition head-on with their development of TLC590. The company has completed a Ph1/2 proof of concept study in hernia repair, comparing the pain management for 4 doses of TLC590 vs immediate-release ropivacaine. In this study the 475 mg dose of TLC590 demonstrated a statistical benefit in pain intensity at both AUC 0-72 and AUC 0-96 vs ropivacaine. In fact, TLC590 showed greater reductions in pain than ropivacaine at every 24-hour interval through 168 hours (AUC 0-168). TLC590 also showed a dramatic reduction in the need for opioids for breakthrough pain compared to ropivacaine. Total opioid use for patients on 450mg TLC590 was 54% less than for those on ropivacaine, and 58% of patients on TLC590 remained opioid-free at the end of

HIGH CONVICTION INVESTMENT IDEA

the study.

The hernia repair study provided early evidence of the potential benefit of TLC590 for postoperative pain management. The pain score and opioid consumption data are highly encouraging, and the duration of benefit is certainly an area of potential future differentiation. In 2019 TLC started a second Ph1/2 study with TLC590, this time in bunionectomy. The Ph1 component was to test the safety and pharmacokinetic (PK) profile of 3 doses (lower doses than in the hernia repair study due to small wound size) of TLC590 vs ropivacaine. After the Ph1 component was completed, the company would take one of the TLC590 doses forward into a Ph2 150-patient efficacy study, where it would be compared against ropivacaine and placebo. The Ph1 component of the study was completed in June 2019, with TLC590 demonstrating favorable PK and a safety profile similar to ropivacaine. TLC elected to take the highest dose of TLC590 tested in Ph1, 228mg, forward for the Ph2 efficacy component of the study. The company also made one important protocol change for Ph2, they switched the active control arm from ropivacaine to bupivacaine. As we noted above, bupivacaine is more commonly used than ropivacaine for the management of postoperative pain. We applaud TLC for making this protocol adjustment and proactively addressing the comparison that we think both medical professionals and investors will be most interested in. TLC announced completion of enrolment in the Ph2 study in February and expects top-line data in May/June.

These Ph2 bunionectomy data will be extremely telling for TLC590. We believe there is a strong probability that TLC590 will show a statistical benefit in pain AUC 0-72 vs both placebo and bupivacaine. Furthermore we think TLC590 could show an extended pain benefit beyond 72-hours, an important area of differentiation. These data will also allow for a loose comparison against Heron's HTX-011 which was tested against bupivacaine in its Ph3 pivotal bunionectomy study. We note that a comparison of TLC's 150-patient Ph2 data vs Heron's >400 patient Ph3 data are not entirely fair, but investors will make the comparison nonetheless.

We think TLC590 is being underappreciated by investors. We like the bold approach the company has taken in Ph2 with the comparison vs bupivacaine. If successful in the Ph2 bunionectomy study, we believe the company will move as quickly as possible into a Ph3 development program.

Financial Considerations

As of YE19 TLC had approximately $34mm in cash. The company also has a $10.358mm loan with Cathay Bank that comes due in June 2020. In our conversations with management, we believe they will put a similar debt instrument in place to repay this existing loan. We estimate the company's cash position is sufficient to fund its operations into 2021. TLC successfully raised equity in 2018 and 2019, and we feel confident that when additional capital is required, likely 2H20, they will be able to raise it.

Notable Risks

Notable risks to our investment thesis include; (1) clinical setbacks in either or both TLC's two prominent clinical programs in pain (TLC599 and TLC590) (2) COVID-19 related risks (i) more profound enrolment delays that what we have forecasted for TLC599's pivotal Ph3 (ii) delays in TLC's ability to start pivotal studies for TLC590 (iii) confounding data due to lack of testing (3) capital market issues, whereby capital becomes challenging and / or excessively expensive to access.

Executive Summary

The Taiwan Liposome Company (TLC) is a clinical-stage specialty pharmaceutical company dedicated to the development and commercialization of novel medicines that combine their proprietary lipid-assembled drug delivery platform with approved active pharmaceutical ingredients (API). Because TLC's product candidates use already approved APIs, they are eligible to utilize the streamlined Food and Drug Administrations 505(b)(2) regulatory pathway for approval in the United States.

TLC have used their proprietary technology platforms, BioSeizer® and NanoX™, to assemble a diverse portfolio of product candidates that target significant areas of unmet medical need including pain management, ophthalmology and oncology. The table below provides a brief summary of TLC's clinical development program areas and product candidates.

TLC's Clinical Development Programs

Product	Technology Platform	Active Pharmaceutical Ingredient	Target	Stage of Development
TLC599	BioSeizer	Dexamethasone Sodium Phosphate	Osteoarthritis	Phase 3
TLC590	BioSeizer	Ropivacaine	Post-surgical Pain Management	Phase 2
TLC399	BioSeizer	Dexamethasone Sodium Phosphate	Macular Edema	Phase 2
TLC178	NanoX	Vinorelbine	Rhabdomyosarcoma	Phase 2
			Soft Tissue Sarcoma	Phase 1

TLC599

TLC is currently developing TLC599 for the treatment of osteoarthritis. Osteoarthritis is the most common form of arthritis and a leading cause of chronic pain and disability affecting approximately 34% of the American population over the age of 65. According to the Arthritis Foundation, in 2015 there were an estimated 30.8 million osteoarthritis patients in the United States.

TLC599 is a proprietary BioSeizer formulation of dexamethasone sodium phosphate designed to provide sustained pain management for up to 24 weeks. Dexamethasone is a synthetic member of the glucocorticoid class of steroid drugs, and has potent anti-inflammatory effects, enhances chondrocyte differentiation and proteoglycan synthesis and reduces glycosaminoglycan loss in injured cartilage.

TLC has examined the effects of TLC599 in two clinical trials (NCT02803307; NCT03005873) and they have two additional trials ongoing (NCT03754049; NCT04123561).

TLC599 Clinical Development Program

Clinical Trial Number	Status	Results
NCT02803307	Completed	Positive clinical results (see section 3.1.2.1)
NCT03005873	Completed	Positive clinical results (see section 3.1.2.2)
NCT03754049	Ongoing	TBD (see section 3.1.2.3)
NCT04123561	Ongoing	TBD (see section 3.1.2.4)

The results from clinical trial NCT02803307 demonstrated that the injection of TLC599 into patients with osteoarthritic knees was well tolerated in all patients with a trend of pain and symptoms relief observed. Clinical trial NCT03005873 demonstrated that TLC599 could provide clinically and statistically significant durable pain relief in patients with knee osteoarthritis through 24 weeks with good tolerability. Furthermore, it was found that over half of the patients treated with TLC599 maintained at least a 30% reduction in pain throughout the duration of the 6-month study (more than twice as much as placebo).

TLC has announced first patient enrollment in its pivotal phase 3 clinical trial (NCT04123561) evaluating single and repeat administrations of TLC599. Following a fruitful end of phase 2 meeting with the FDA, TLC believes that the successful completion of the phase 3 trial should be sufficient to support a New Drug Application submission.

TLC590

TLC is developing TLC590 as a local anesthetic for post-surgical pain management. The goal of this product is to reduce the frequency of administration of local anesthesia for post-surgical pain. According to statistics from the Centers for Disease Control and Prevention, approximately 100 million surgical procedures are performed in the United States each year. Managing acute post-surgical pain is a major challenge for practitioners, given that more than 80% of patients report pain after surgery, and 75% report the pain as moderate, severe, or even extreme. In more than half of cases, patients report not receiving adequate pain management following their procedure, which raises concerns over the development of chronic pain in the future.

TLC590 is a sustained release delivery technology for the common anesthetic ropivacaine. Ropivacaine is currently FDA approved for surgical anesthesia and acute pain management and has a few properties that make it unique. Ropivacaine is less lipophilic than other local anesthetics, such as bupivacaine, and is less likely to penetrate large myelinated motor fibers. It selectively acts on the nociceptive A, B, and C fibers over the AB (motor) fibers and is manufactured as a pure S(-) enantiomer. This is an advantage since the S(-) enantiomer has significantly less cardiotoxicity and neurotoxicity.

TLC has examined the clinical effects of TLC590 in one clinical trial (NCT03591146) and has one additional ongoing trial (NCT03838133).

TLC590 Clinical Development Program

Clinical Trial Number	Status	Results
NCT03591146	Completed	Positive results (see section 3.2.2.1)
NCT03838133	Ongoing	TBD (see section 3.2.2.2)

In clinical trial NCT03591146, TLC590 showed a similar safety and tolerability profile to the approved drug Naropin (immediate-release ropivicaine), with no local anesthetic systemic toxicity events. It yielded more immediate and long-lasting pain reduction than Naropin, reducing or eliminating the need for opioids after inguinal hernia repair surgery. Patients receiving the highest dose of TLC590 tested, showed superiority to Naropin, with lower mean pain scores at all points and significantly reduced total pain at various time intervals through four days post-surgery.

TLC has recently announced top line results from Part 1 of a TLC590 phase 2 clinical trial (NCT03838133) for post-surgical pain management following bunionectomy. The key findings from the analysis were:

- Dose linearity and relative bioavailability of TLC590 have been established.
- All three doses of TLC590 were well tolerated, with a safety profile comparable to Naropin.
    - Most treatment-emergent adverse events were mild to moderate in severity.
    - There were no treatment-related or serious adverse events and no adverse events leading to with-drawal.

The TLC590 228 mg dose was chosen to move forward with in Part 2 of the trial based on maximum feasible volume for bunionectomy. TLC also changed the active comparator arm from Naropin to bupivacaine for Part 2 of the study.

TLC399

TLC is currently developing TLC399 as an intravitreal (eye) injection for the treatment of macular edema due to retinal vein occlusion. Macular edema with retinal vein occlusion is a disease of the retina that causes impaired vision, characterized by leakage of fluid from the blood vessels in the retina. Worldwide, it is estimated that 16.4 million people have had a retinal vein occlusion with approximately 180,000 new retinal vein occlusions cases in the United States each year.

TLC399 utilizes TLC's BioSeizer technology to allow for sustained release of dexamethasone in the eye and is specifically designed to provide effects lasting as long as six months between injections. So far TLC has studied the clinical effects of TLC399 in one clinical trial (NCT02006147) and an additional clinical trial is planned (NCT03093701).

TLC399 Clinical Development Program

Clinical Trial Number	Status	Results
NCT02006147	Ongoing	TBD (see section 3.3.2.1)
NCT03093701	Ongoing	TBD (see section 3.3.2.2)

TLC has stated that clinical trial NCT02006147 has demonstrated encouraging signs of efficacy in both the reduction of retinal central subfield thickness and improvements in visual acuity. However, no additional results are available publicly at this time.

TLC178

TLC178 is a proprietary NanoX formulation of the drug vinorelbine, that is being developed for the treatment of cancer. TLC is currently completing a traditional 3+3 Ph1 study with TLC178 in patients with advanced malignancies. Safety, dosing an preliminary efficacy from this study will inform the company on how it could potentially proceed into later stage studies in rhabdomyosarcoma, soft tissue sarcoma and non-small cell lung cancer.

Conclusion

TLC has extensive experience with liposome science which has allowed them to combine the benefits of fast drug onset speed and extended duration. In addition, their technology has improved API concentrations at target tissues while decreasing unwanted systemic exposures. TLC have used their proprietary technology platforms to assemble a diverse portfolio of product candidates that target significant areas of unmet medical need. Their lead candidate TLC599 is currently being tested in a pivotal phase 3 trial, which if successful is expected to lead to the submission of a New Drug Application with the FDA.

Table of Contents

List of Tables

List of Figures

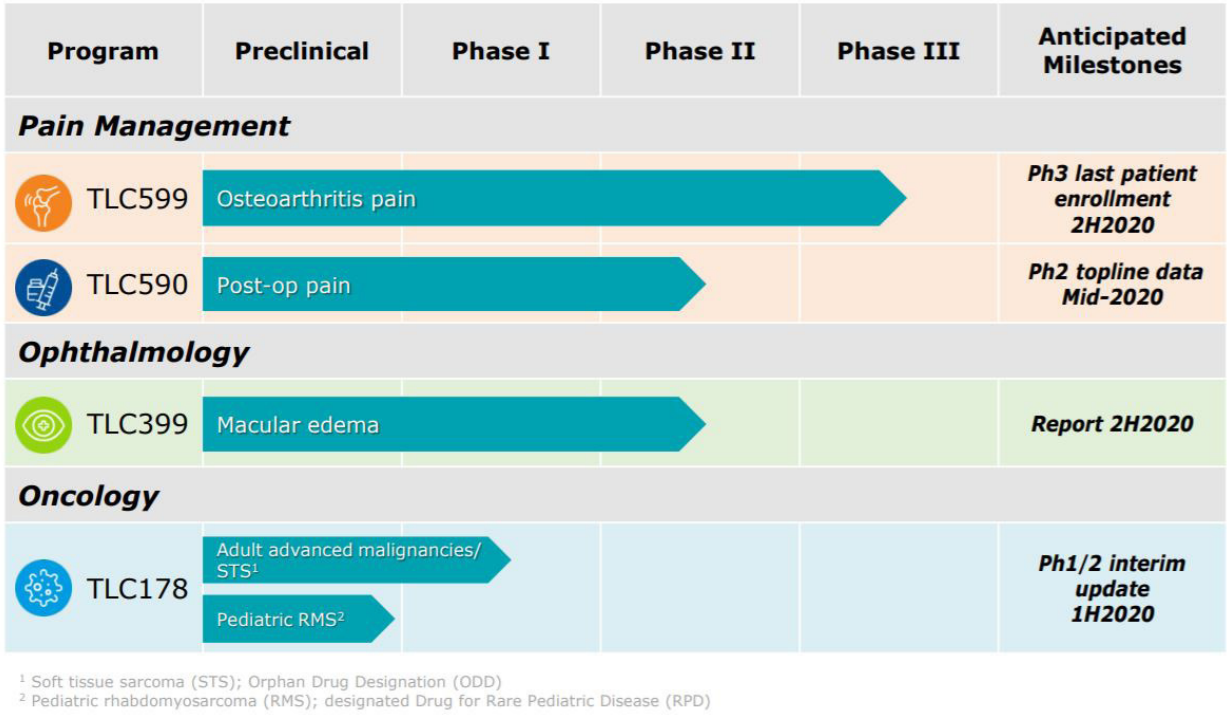
1 Introduction

1.1 Taiwan Liposome Company

The Taiwan Liposome Company (TLC) is a clinical-stage specialty pharmaceutical company dedicated to the development and commercialization of best-in-class novel nanomedicines that combine their proprietary lipid-assembled drug delivery platform with approved active pharmaceutical ingredients (APIs). Because TLC's product candidates use already approved APIs, they are eligible to utilize the streamlined Food and Drug Administrations (FDA) 505(b)(2) regulatory pathway for approval in the United States (US).

TLC currently has four assets, in three program areas, at various stages in development (Figure 1). The program areas include pain management (TLC599, TLC590), ophthalmology (TLC399) and oncology (TLC178).

Figure 1 Summary of TLC's Clinical Development Programs



(Yeh, Corporate Presentation)

TLC have two proprietary technology platforms, BioSeizer® and NanoX™, which they have used to assemble their diverse portfolio of product candidates.

1.2 BioSeizer®

TLC has a proprietary solution for pharmaceutical product development called BioSeizer. The BioSeizer technology uses multi-layer lipid membranes to encapsulate therapeutically active molecules, providing an exceptionally long duration of drug release. BioSeizer nanoparticles are precisely designed to release their payload at a constant rate as each layer collapses over time. In addition, BioSeizer works to extend the duration of therapies based on both small molecules as well as large, biologic molecules.

The advantages of the BioSeizer technology to include:

- Versatile for delivering drugs such as antibodies, Fab, scFv, peptide, aptamer, DNA, siRNA and small molecules,
- Able to design the API's releasing profile,

- Provides immediate availability of free API,
- Prolongs the retention time of APIs at the disease site,
- Reduces the side effects of APIs due to systemic exposure,
- Fully biodegradable components,
- Protected by composition of matter patents.

Unlike other extended-release formulations, BioSeizer formulations are not implants or large-size particles. Rather, BioSeizer formulations allow local injections into sensitive tissues such as the eye or inflamed joints using much smaller gauge needles.

The BioSeizer technology is currently being utilized in TLC's TLC599, TLC590 and TLC399 programs (Figure 1).

1.3 NanoX™

TLC also has a proprietary solution for pharmaceutical product development called NanoX. The NanoX technology uses nanoparticles coated with the compound polyethylene glycol to reduce uptake by phagocytic cells of the immune system. This prolongs circulation in the body and allows the drug to predominantly accumulate at disease sites such as tumors. Therapies based on the NanoX technology can also make use of additional molecular coatings to help nanoparticles to accumulate at cells of a specific type, such as tumor cells.

The advantages of the NanoX technology to include:

- Efficient encapsulation of various drugs in liposomes,
- Greater stability to support longer shelf-life,
- Prolonged circulation time (t½) by decreased clearance,
- Potential for decreased toxicity due to preferential distribution to tumor tissue,
- Able to be applied to both small and large molecules,
- No exposure to organic solvents, which might lead to denaturation of the protein API, during the manufacturing process,
- A robust, scalable and replicable manufacturing process.

NanoX could also be developed as an antibody-conjugated variant for next-generation tissue/cellular targeting delivery. Furthermore, TLC believes that the payload-antibody ratio for antibody-conjugated NanoX could reach over 50, an order of magnitude improvement in efficiency over a conventional ratio of less than eight.
The NanoX technology is currently utilized by TLC's TLC178 program (Figure 1).

1.4 Report Objective

The objective of this report is to summarize the information available on TLC's proprietary technology and portfolio of product candidates. This information will then be used to determine the potential future commercial prospects for TLC and its products.

2 Literature Search

Pubmed searches (https://www.ncbi.nlm.nih.gov/pubmed) using the following keys words were performed by the author in December of 2019:

- BioSeizer
- TLC599
- Dexamethasone, DEX, DSP
- Osteoarthritis, OA
- TLC590
- Ropivacaine, Naropin
- Post-surgical Pain, Post Operative Pain
- TLC399
- Macular Edema
- Retinal Vein Occlusion, RVO, BRVO, CRVO
- NanoX

- TLC178
- Vinorelbine
- Rhabdomyosarcoma, RMS
- Soft Tissue Sarcoma, STS

Abstracts were reviewed for their relevance and if available free online, the full article was obtained. The pubmed searches were restricted to information available for humans. No time restrictions were imposed. Additional references, identified through article review, were also included if deemed relevant.

In addition to the pubmed searches, information from the following websites was also reviewed:

- TLC - https://www.tlcbio.com/en-global/overview/index
- Clinical Trials Government - https://clinicaltrials.gov
- Drug Information Portal - https://druginfo.nlm.nih.gov/drugportal
- U.S. Food and Drug Administration - https://www.fda.gov

A comprehensive list of references used for compiling this report can be found in section 5.

3 Discussion

3.1 TLC599

3.1.1 Background

TLC is currently developing TLC599 for the treatment of osteoarthritis (OA). OA is the most common form of arthritis and a leading cause of chronic pain and disability (Lim et al, 2012) affecting approximately 34% of the US population over age 65 (Lawrence et al, 2008). According to the Arthritis Foundation, there were an estimated 30.8 million OA patients in the US in 2015, with the number of patients expected to continue to grow.
OA can occur in any synovial joint, but the knee, hip, and joints of the hand are most commonly affected (Martel-Pelletier et al, 2016; Johnson et al, 2014). Important risk factors for the development of OA include increasing age, female gender, previous joint trauma, and genetic factors (Martel-Pelletier et al, 2016; Spector et al, 2004). In addition, increased mechanical stress on the joints caused by factors, such as malalignment (Martel-Pelletier et al, 2016), increased body weight (Felson et al, 1988; Gelber et al, 1999), and manual work (Jensen, 2008a; Jensen, 2008b; Kaila-kangas et al, 2011), also play an important role. While the signature characteristic of OA is a loss of articular cartilage, it is apparent that many other joint structures can become affected as the disease progresses, including the subchondral bone, fibrocartilage, capsule, ligaments, synovial membrane, and periarticular muscles (Madry et al, 2012; Scanzello et al, 2012; Kapoor et al, 2011).

OA is managed using pharmacological and non-pharmacological approaches. When these fail, surgical interventions such as joint replacement are considered. Analgesics including paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs, topical and oral) and opioid medications are the primary pharmacological treatments for symptomatic OA. However, NSAIDs and opioids are unsuitable for many patients given their side effect profile and because the benefits from paracetamol and opioids are limited (Zhang et al, 2010).
Intra-articular (IA) therapies are also commonly used in clinical practice, though often with short-term benefits. Common IA therapies include (Ghouri et al, 2019):

- Intra-articular capsaicin,
- Injectable corticosteroids, and
- Intra-articular triamcinolone acetonide extended-release.

Despite the use of currently available IA treatments, many OA patients experience persistent and worsening pain. Therefore, there exists a need for a safe alternative treatment that could provide both rapid and sustained relief from OA pain and potentially delay the need for joint replacement surgery.

TLC599 is TLC's proprietary BioSeizer formulation of dexamethasone sodium phosphate (DSP) designed to provide sustained pain management for up to 24 weeks. Dexamethasone is a synthetic member of the glucocorticoid class of steroid drugs, with a potency about 20–30 times that of the naturally occurring

hydrocortisone and 4–5 times that of another widely used synthetic analog, prednisolone (Hollander, 1960). Dexamethasone is a broad-spectrum corticosteroid which has potent anti-inflammatory effects, enhances chondrocyte differentiation and proteoglycan synthesis and reduces glycosaminoglycan loss in injured cartilage in vitro (Grodzinsky et al, 2017; Li et al, 2015; Lu et al, 2011) and in vivo (Huebner et al, 2014; Malfait et al, 2009).

3.1.2 Clinical Trials

The effects of TLC599 have been examined in two clinical trials (NCT02803307; NCT03005873) and two additional clinical trials are ongoing (NCT03754049; NCT04123561) (Table 1). The designs of these trials have been outlined in the sections below and where available trial results have been provided.

Table 1 Clinical Program for TLC599

Clinical Trial Number	Status	Results
NCT02803307	Completed	Available
NCT03005873	Completed	Available
NCT03754049	Recruiting	Not Yet Available
NCT04123561	Recruiting	Not Yet Available

3.1.2.1 NCT02803307

Clinical trial NCT02803307 is a phase 1/2, multi-site, randomized, open-label, parallel-design, single-dose study. The objective of the trial was to investigate the safety and efficacy of TLC599 in subjects with OA of the knee. A brief outline of the study can be found in Table 2.

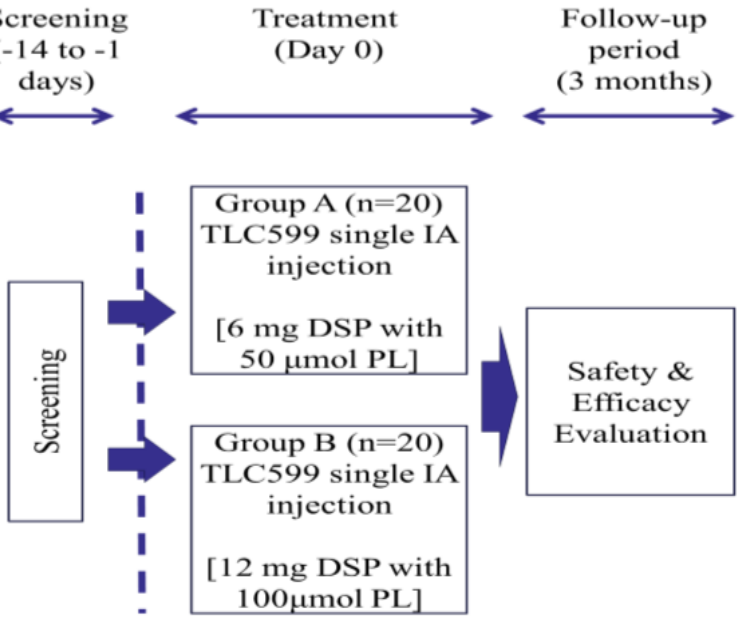
Table 2 NCT02803307 Clinical Trial Design

Clinical Trial NCT02803307	
Title	A Randomized, Open-label, Parallel, Phase I/II Single-Dose Administration Trial of TLC599 in Subjects with Osteoarthritis of the Knee
Type	Interventional
Phase	Phase 1 Phase 2
Design	• Allocation: Randomized • Intervention Model: Parallel Assignment • Masking: None (Open Label) • Primary Purpose: Treatment
Condition	Osteoarthritis of the knee
Intervention	Drug: TLC599 Single dose via intra-articular injection

Clinical Trial NCT02803307	
Arms	• Experimental: 6 mg TLC599 6 mg DSP with 50 µmol PL Intervention: Drug: TLC599 • Experimental: 12 mg TLC599 12 mg DSP with 100 µmol PL Intervention: Drug: TLC599
Primary Outcome	Safety parameters [Time Frame: up to 12 weeks after dosing] Safety parameters will be assessed as measured by adverse events (AEs), changes in physical examinations, vital signs, and clinical laboratory results
Secondary Outcomes	• Pain score (VAS) [Time Frame: Questionnaire will be collected at baseline, Week 1, Week 4, Week 8, Week 12] • WOMAC questionnaire [Time Frame: Questionnaire will be collected at baseline, Week 1, Week 4, Week 8, Week 12] • IGART questionnaire [Time Frame: Questionnaire will be collected at Week 1, Week 4, Week 8, Week 12]
Enrollment	40
Location	Taiwan
Status	Completed
Sponsor	Taiwan Liposome Company
Investigator(s)	Not provided
AE = Adverse Event; DSP= Dexamethasone Sodium Phosphate; IGART = Investigator's Global Assessment of Response to Therapy; PL = Phospholipid; VAS = Pain Score in Visual Analogue Scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index	

In clinical trial NCT02803307, 40 subjects with knee OA were randomized to one of two TLC599 dose groups (A and B), at three sites (Taipei Veterans General Hospital, Mackay Memorial Hospital, and Taipei Medical University Hospital) in Taiwan. Group A patients (n = 20) were treated with 6 mg DSP with 50 µmol phospholipid (PL) and Group B patients (n = 20) were treated with 12 mg DSP with 100 µmol PL (Figure 2).

Figure 2 Schematic Representation of Clinical Trial NCT02803307 Design



(Lai et al, 2018)

Demographic information from the study is summarized in Table 3 (Lai et al, 2018).

Table 3 Demographic Information from Clinical Trial NCT02803307

		Group A 6 mg DSP	Group B 12 mg DSP	All
Number of Patients		20	20	40
East Asian (Race)		20	20	40
Gender	Male	2	6	8
	Female	18	14	32
Age	Mean	66.7	68.1	67.4
	Median	67.5	69.5	68.5
	Minimum	49	52	49
	Maximum	89	84	89
DSP= Dexamethasone Sodium Phosphate				

(Lai et al, 2018)

Safety

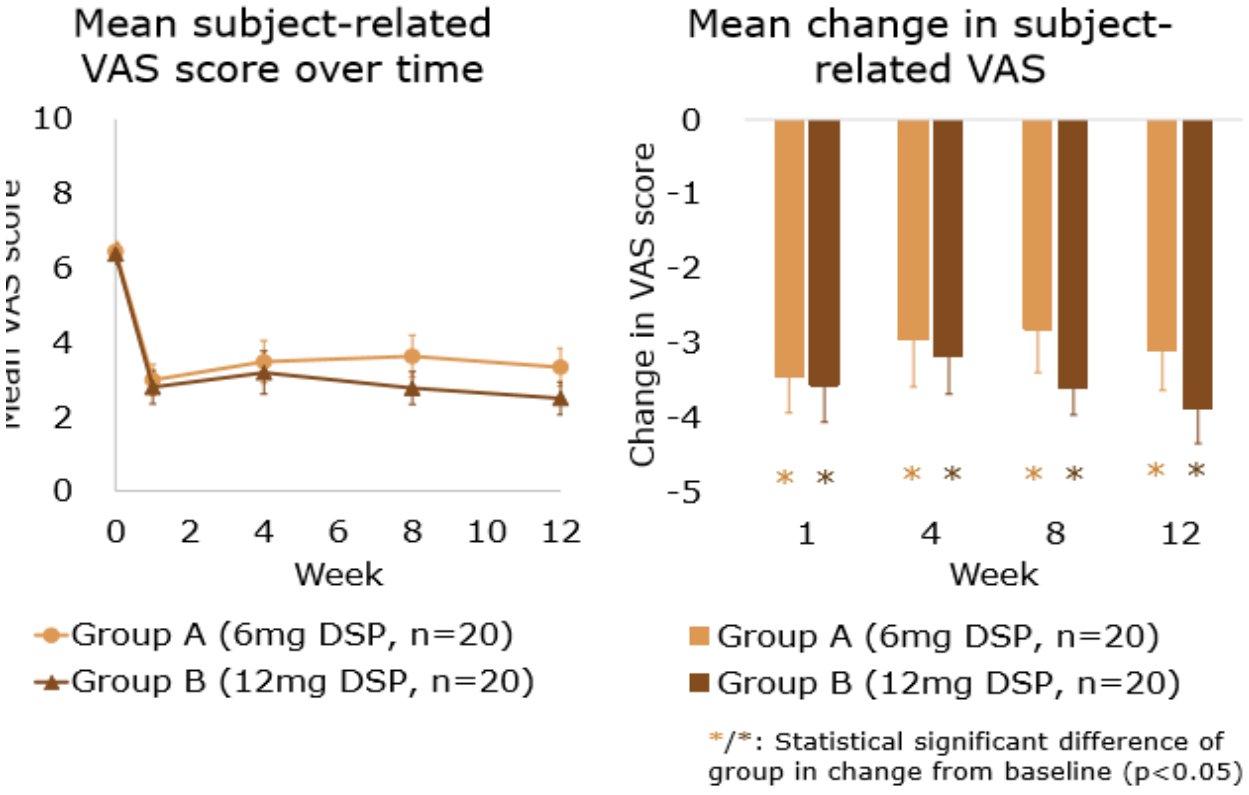
No serious adverse events (SAE), important adverse events (AE), or AEs leading to withdrawal occurred during this study. No significant changes in mean HbA1c were observed over the 12-week trial. Only two treatment-related adverse events of grade 1 hyperglycemia were reported in two Group B subjects. Mean plasma cortisol was transiently decreased after TLC599 dosing. The decreased cortisol levels were within the normal range at all time points studied (Lai et al, 2018).

Efficacy

Mean patient pain score in visual analog scale (VAS) (Figure 3) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale (Figure 4) showed sustained decreases from baseline in both Group A and Group B starting at week 1 through the end of study at week 12 (Lai et al, 2018).

The VAS is a reliable, valid, responsive, and frequently used pain outcome measure (Hjermstad et al, 2011). It consists of a bidirectional 10 cm straight line with two labels, that is, "no pain" and "worst possible pain", located at either end of the line. Patients are instructed to draw a vertical mark on the line indicating their pain level (Hjermstad et al, 2011). VAS has excellent test–retest reliability with small error in the measurement of OA knee pain (Alghadir et al, 2018).

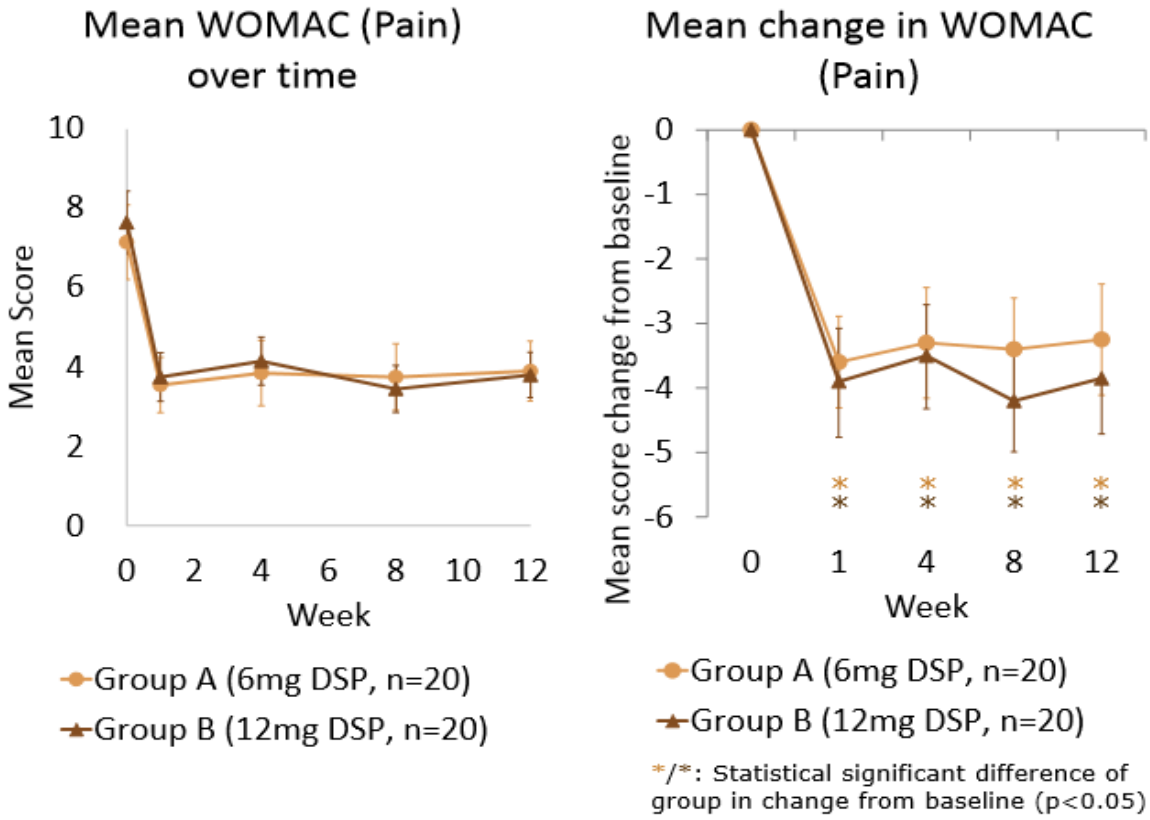
Figure 3 Mean Subject-reported VAS Through 12 Weeks (Intent to Treat Population)



(Lai et al, 2018)

The WOMAC Index is one of the most common patient reported outcome assessments (PROs) for evaluating pain, stiffness, and function in patients with knee OA. The measure was developed to evaluate clinically important, patient relevant changes in health status as a result of treatment intervention (Bellamy, 1995). The WOMAC Index comprises 24 questions that ask how patients perceive their OA-related knee pain (n = 5), stiffness (n = 2), and function (n = 17) during specific activities (Roos et al, 1999; Bellamy et al, 1986), as well as two additional questions that allow patients to rate their overall pain in each knee over the past 48 hours. Bellamy and colleagues provided evidence of the reliability (test–retest), validity, and responsiveness of the WOMAC in OA patients undergoing total knee or hip arthroplasty (Bellamy et al, 1988a) and in OA patients receiving NSAIDs (Bellamy et al, 1988b). Subsequently McConnell et al (2001) reviewed the utility and measurement properties of WOMAC.

Figure 4 Mean WOMAC Pain Through 12 Weeks (Intent to Treat Population)



(Lai et al, 2018)

Over 50% of the patients displayed clinical response at all time points through 12 weeks for both dose levels (Table 4). The clinical responder rate was calculated based on OMERACT-OARSI's responder criteria (Pham et al, 2004). Responder is defined as a ≥ 50% improvement and absolute improvement of ≥ 20 points from baseline in VAS or WOMAC physical function subscale. Subjects were also considered responders when VAS pain ≥ 20% and absolute change ≥10 with WOMAC physical function ≥20% and absolute change ≥ 10 (Lai et al, 2018).

Table 4 Percentage of Clinical Responders Through 12 Weeks

	Group A 6 mg DSP (n=20)	Group B 12 mg DSP (n=20)
Week 1	70%	75%
Week 4	70%	65%
Week 8	70%	85%
Week 12	70%	75%
DSP= Dexamethasone Sodium Phosphate		

(Lai et al, 2018)

In conclusion, clinical trial NCT02803307 demonstrated that the injection of TLC599 into the OA knee was well tolerated in all patients and a trend of pain and symptoms relief was observed in both treatment groups.

3.1.2.2 NCT03005873

Clinical trial NCT03005873 was a phase 2a, randomized, double-blinded, placebo-controlled, dose-finding study. The objective of the trial was to investigate the safety and efficacy of TLC599 in subjects with OA of the knee. A brief outline of the study can be found in Table 5.

Table 5 NCT03005873 Clinical Trial Design

Clinical Trial NCT03005873	
Title	A Phase IIa, Randomized, Double Blinded, Placebo Controlled, Dose Finding Study for Single Dose Administration of TLC599 in Patients with Osteoarthritis (OA) of Knee
Type	Interventional
Phase	Phase 2
Design	• Allocation: Randomized • Intervention Model: Parallel Assignment • Masking: Double (Participant, Investigator) • Primary Purpose: Treatment
Condition	Osteoarthritis of the knee
Intervention	• Drug: TLC599 LD group Single dose via intra-articular injection Other Name: 12 mg DSP with 100 µmol PL (1.0 mL) • Drug: Normal Saline Single-dose via intra-articular injection Other Name: Placebo • Drug: TLC599 HD group Single-dose via intra-articular injection Other Name: 18 mg DSP with 150 µmol PL (1.5 mL)
Arms	• Experimental: TLC599 LD group 12 mg DSP with 100 µmol PL (1.0 mL) Intervention: Drug: TLC599 LD group • Experimental: TLC599 HD group 18 mg DSP with 150 µmol PL (1.5 mL) Intervention: Drug: TLC599 HD group • Placebo Comparator: Placebo group 1.5 mL normal saline Intervention: Drug: Normal Saline
Primary Outcome	• WOMAC questionnaire pain sub-scale [Time Frame: from dosing through Week 12] The primary endpoint is to evaluate the change from baseline by Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale through Week 12.

Clinical Trial NCT03005873	
Secondary Outcomes	• WOMAC questionnaire pain sub-scale [Time Frame: at Weeks 1, 4, 8, 12, 16, 20, and 24] Change from baseline to Weeks 1, 4, 8, 12, 16, 20, and 24 in pain/function subscales of WOMAC. • Pain score (VAS) [Time Frame: at Weeks 1, 4, 8, 12, 16, 20, and 24] Change from baseline to Weeks 1, 4, 8, 12, 16, 20, and 24 in the patient-rated visual analog scale (VAS). • Pain score (VAS) [Time Frame: from dosing through Week 12, 16, 20, 24] Change from baseline through Weeks 12, 16, 20, and 24 in the patient-rated visual analog scale (VAS). • WOMAC questionnaire pain sub-scale [Time Frame: from dosing through Week 12, 16, 20, 24] Change from baseline through Weeks 12, 16, 20, and 24 in the patient-rated visual analog scale (VAS). • EuroQol-5 Dimension questionnaire [Time Frame: at Weeks 1, 4, 8, 12, 16, 20, and 24] Change from baseline to Weeks 1, 4, 8, 12, 16, 20, and 24 in EuroQol-5 Dimension questionnaire. • Usage of acetaminophen [Time Frame: at Weeks 1, 4, 8, 12, 16, 20, and 24] Total consumption of acetaminophen at Weeks 1, 4, 8, 12, 16, 20, and 24. • Incidence of Treatment-Emergent Adverse Events [Time Frame: up to 24 weeks after dosing] To evaluate the safety and tolerability of TLC599 by incidence of Treatment-Emergent Adverse Events reported by Investigators
Enrollment	77
Location	Australia Taiwan
Status	Completed
Sponsor	Taiwan Liposome Company
Investigator	Study Director: Yvonne Shih, PhD Taiwan Liposome Company
OA = Osteoarthritis; VAS = Pain Score in Visual Analogue Scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index	

In clinical trial NCT03005873, participants were 50 years old or older, with Kellgren-Lawrence Grade 2-3 knee OA and pain severity of 5-9 on the visual analog scale. Patients were randomized to receive a single IA injection of TLC599 12 mg (12 mg DSP with 100 µmol phospholipid), TLC599 18 mg (18 mg DSP with 150 µmol phospholipid), or placebo (saline). A total of 149 participants were screened and 75 received treatment. For each patient, only one knee was selected for study drug injection. All participants were scheduled for follow-up at 24 weeks post injection (Hunter et al, 2018).

Demographic information from the study can be found in Table 6.

Table 6 Demographic Information from Clinical Trial NCT03005873

		Placebo (n=25)	TLC599 12 mg (n=26)	TLC599 18 mg (n=24)
Age	Average	64.8 (8.45)	63.9 (9.07)	62.9 (8.80)
	≥ 66 Years	11 (44.0%)	10 (38.5%)	9 (37.5%)
Gender	Male	28%	42.3%	29.2%
	Female	72%	57.7%	70.8%
Race	Asian	12 (48.0%)	13 (50.0%)	12 (50.0%)
	Caucasian	13 (52.0%)	13 (50.0%)	11 (45.8%)
Knee OA	Unilateral	40%	38.5%	38.7%
	Bilateral	60%	61.5%	61.3%
K-L Grade	2	36%	50%	37.5%
	3	64%	50%	62.5%

(Yeh, Corporate Presentation)

Safety

Treatment-emergent adverse events (TEAEs) among the three groups (TLC599 12 mg, TLC599 18 mg, and placebo) were comparable. There were no life-threatening treatment related TEAEs or unexpected safety signals. No deaths or treatment-related serious adverse events (SAEs) occurred during the study (Hunter et al, 2018). Safety information from the study can be found in Table 7.

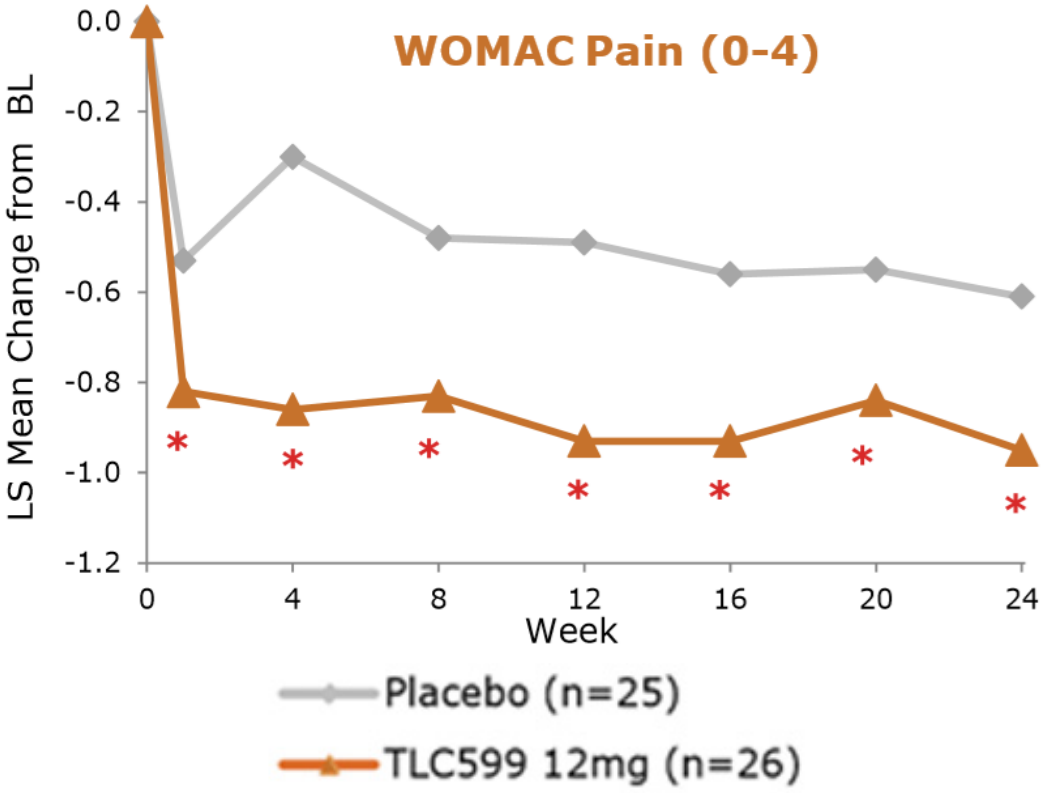
Table 7 Safety Information from Clinical Trial NCT03005873

	Placebo (n=25)	TLC599 12 mg (n=26)	TLC599 18 mg (n=24)
TEAE	17 (68%)	18 (69.2%)	20 (83.3%)
Treatment-related TEAE	4 (16%)	7 (26.9%)	11 (45.8%)
Treatment-related SAE	0	0	0
Index Knee-related TEAE	4 (16%)	1 (3.8%)	3 (12.5%)
TEAE Related to Procedure Injection	3 (12%)	1 (3.8%)	3 (12.5%)
SAE = Serious Adverse Event; TEAE = Treatment Emergent Adverse Event			

Efficacy

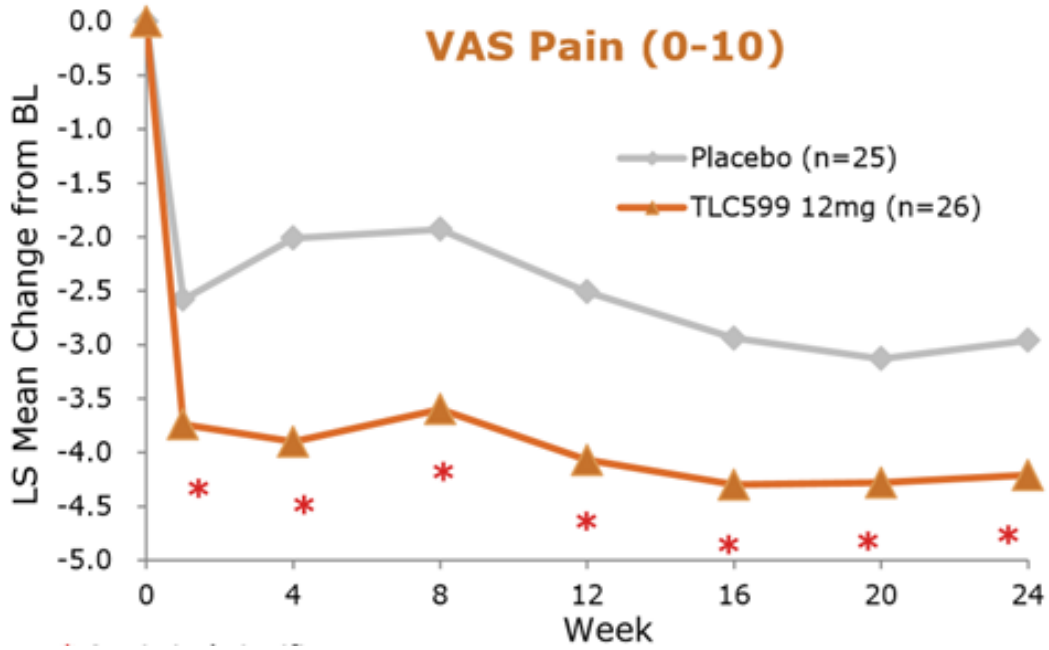
The mean WOMAC (0-4 scale)/VAS (0.0 - 10.0 scale) pain scores at baseline in placebo, TLC599 12 mg and TLC599 18 mg groups were 1.6/6.6, 1.5/6.5 and 1.7/6.9, respectively. Although both placebo- and TLC599-treated patients displayed a reduction in WOMAC pain score, those treated with TLC599 12 mg displayed a significantly greater reduction than placebo through all specified time points, including weeks 12, 16, 20 and 24 ($p<0.05$) (Figure 5) (Hunter et al, 2018). Similar trends were observed in VAS pain scores (Figure 6) (Hunter et al, 2018).

Figure 5 WOMAC Pain (0-4) Change from Baseline



(Yeh, Corporate Presentation; Hunter et al, 2018)

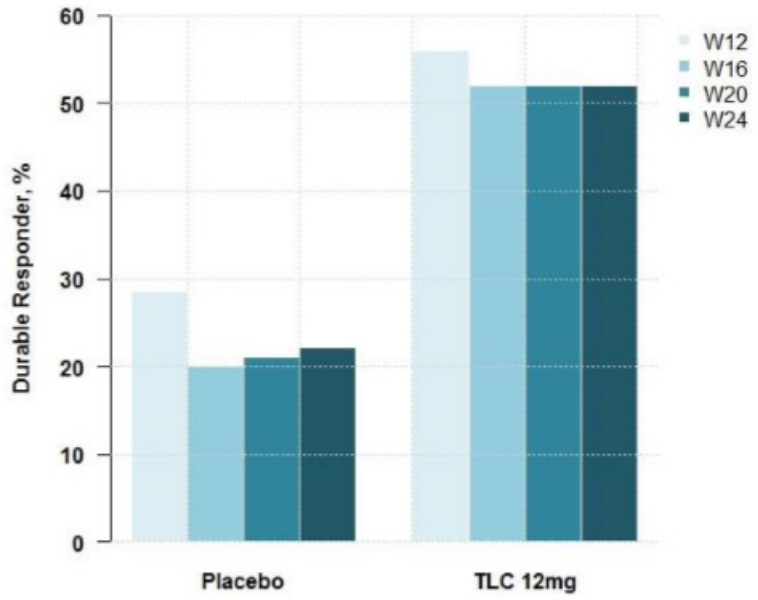
Figure 6 VAS Pain (0-10) Change from Baseline



(Yeh, Corporate Presentation)

A majority of the TLC599 12 mg group had a durable response, maintaining at least 30% pain relief at all visits from week 1 through week 12 (56% vs 29% in placebo; p=0.0104) and further through week 24 (52% vs 22% in placebo; p=0.0143) (Figure 7) (Hunter et al, 2018).

Figure 7 Proportions of Durable Responders with Persistent Response



*Persistent response is defined by pain relief > 30% in WOMAC pain subscale over time

(Hunter et al, 2018)

The onset of pain relief started as early as day 3 post-dose, with no sign of loss in pain relief noted at week 24. Reductions in pain with TLC599 18 mg group were not as great as with TLC599 12 mg group. In addition, a trend of lower total consumption of acetaminophen was observed in the TLC599-treated groups compared to the placebo group through week 24 (Hunter et al, 2018).

In conclusion, clinical trial NCT03005873 demonstrated that TLC599 12 mg could provide clinically and statistically significant durable pain relief in participants with knee OA through 24 weeks with good tolerability. Furthermore, over half of participants treated with TLC599 12 mg maintained at least a 30% reduction in pain throughout the 6-month study period (more than twice the placebo).

3.1.2.3 NCT03754049

Clinical trial NCT03754049 is an ongoing, single-center, phase 2, open-label, 1-period, parallel study. Nine cohorts of patients with OA of the knee will be enrolled to receive a single-dose of TLC599 or DSP via IA injection. A brief outline of the study can be found in Table 8.

Table 8 NCT03754049 Clinical Trial Design

Clinical Trial NCT03754049	
Title	A Phase 2, Open-label, Pharmacokinetic Study of a Single Intra-articular Administration of TLC599 in Subjects with Mild to Moderate Osteoarthritis of the Knee
Type	Interventional
Phase	Phase 2
Design	• Allocation: Non-Randomized • Intervention Model: Parallel Assignment • Masking: None (Open Label) • Primary Purpose: Treatment
Condition	Osteoarthritis of the knee
Intervention	• Drug: TLC599 TLC599 is manufactured with the proprietary lipid formulation in the lyophilized form (BioSeizer) for the reconstitution with the aqueous DSP (active ingredient). Other Name: TLC599 Injection • Drug: DSP Dexamethasone sodium phosphate (DSP) is a glucocorticoid widely used in the treatment of joint pain such as gout, osteoarthritis and rheumatoid arthritis via IA injection. Other Name: Dexamethasone Sodium Phosphate
Arms	• Experimental: TLC599 12 mg 12 mg DSP with 100 µmol phospholipid via IA injection; Intervention: Drug: TLC599 • Experimental: TLC599 6 mg 6 mg DSP with 50 µmol phospholipid via IA injection. Intervention: Drug: TLC599 • Active Comparator: DSP 4mg Dexamethasone Sodium Phosphate (DSP): 4 mg/mL, 1 mL via IA injection. Intervention: Drug: DSP
Primary Outcome	• Area under the Curve [AUC] [Time Frame: Baseline till 24 weeks post IP administration] Area under the concentration-time curve • Cmax: maximum concentration [Time Frame: Baseline till 24 weeks post IP administration] Maximum concentration • Tmax: time to peak concentration [Time Frame: Baseline till 24 weeks post IP administration] Time to peak concentration
Secondary Outcomes	• Number of AEs, including SAE and treatment-emergent AE [Time Frame: Screening till 25 weeks post IP administration] • Number of AEs, including SAE and treatment-emergent AE Cortisol concentration [Time Frame: baseline till 24 weeks post IP administration] Cortisol concentration
Enrollment	90
Location	United States
Status	Recruiting

Clinical Trial NCT03754049	
Sponsor	Taiwan Liposome Company
Investigator	Study Director: Carl Brown, PhD Taiwan Liposome Company
AE = Adverse Event; AUC = Area Under the Concentration Curve; Cmax = Maximum Concentration; DSP = Dexamethasone Sodium Phosphate; IA = Intra-articular; SAE = Serious Adverse Event; Tmax = Time to Peak Concentration	

This trial is currently recruiting patients. No results are publicly available at this time.

3.1.2.4 NCT04123561

Clinical trial NCT04123561 is an ongoing, phase 3, randomized, double-blind, placebo- and active comparator-controlled pivotal study. Approximately 500 adult patients with moderate to severe pain due to OA of the knee will be enrolled and randomized. All patients will be followed for a total of 52 weeks. Efficacy and safety of two doses of TLC599 will be evaluated in comparison to placebo and DSP throughout the trial. A brief outline of the study can be found in Table 9.

Table 9 NCT04123561 Clinical Trial Design

Clinical Trial NCT04123561	
Title	A Phase 3, Randomized, Double-blind, Placebo- and Active-controlled Study to Evaluate the Efficacy and Safety of TLC599 in Patients with Osteoarthritis of the Knee
Type	Interventional
Phase	Phase 3
Design	• Allocation: Randomized • Intervention Model: Parallel Assignment • Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) • Primary Purpose: Treatment
Condition	Osteoarthritis of the knee

Clinical Trial NCT04123561	
Intervention	• Drug: TLC599 TLC599 is a proprietary (Bioseizer) lipid formulation containing DSP (active ingredient) Other Name: TLC599 Injection • Drug: DSP Dexamethasone sodium phosphate (DSP) is a glucocorticoid widely used in the treatment of joint pain such as gout, osteoarthritis and rheumatoid arthritis via IA injection. Other Name: Dexamethasone Sodium Phosphate • Other: Normal Saline 0.9% normal saline
Arms	• Experimental: TLC599 TLC599 (1mL) IA injection Intervention: Drug: TLC599 • Active Comparator: Dexamethasone sodium phosphate DSP 4mg (1mL) IA injection Interventions: Drug: TLC599 Drug: DSP • Placebo Comparator: Normal Saline Normal saline (1mL) IA injection Intervention: Other: Normal Saline
Primary Outcome	• Change from Baseline in WOMAC Pain [Time Frame: Baseline, Week 16] Change from Baseline in WOMAC Pain
Secondary Outcomes	• Change from Baseline in WOMAC Pain [Time Frame: up to Week 52] Change from Baseline in WOMAC Pain • Change from Baseline in WOMAC Function [Time Frame: up to Week 52] Change from Baseline in WOMAC Function • Patient Global Impression of Change (PGIC) [Time Frame: up to Week 52] Patient Global Impression of Change (PGIC) • Consistent responder status defined as WOMAC Pain score <1.2 [Time Frame: Week 16, Week 40] Consistent responder status defined as WOMAC Pain score <1.2 0-4
Enrollment	500
Location	Not provided
Status	Not yet recruiting
Sponsor	Taiwan Liposome Company
Investigator	Study Director: Carl Brown, PhD Taiwan Liposome Company

Clinical Trial NCT04123561
DSP = Dexamethasone Sodium Phosphate; IA = Intra-articular; PGIC = Patient Global Impression of Change; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

TLC has announced first patient enrollment in its phase 3 clinical trial evaluating single and repeat administrations of TLC599 (TLC Press Release, October 01, 2019). After a successful end of phase 2 meeting with the FDA, TLC believes that the phase 3 trial will be sufficient to support a New Drug Application (NDA) submission (TLC Press Release, April 15, 2019).

3.2 TLC590

3.2.1 Background

TLC is currently developing TLC590 as a local anesthetic for post-surgical pain management. The goal of this product is to reduce the frequency of administration for local anesthesia for post-surgical pain. According to statistics from the Centers for Disease Control and Prevention (CDC), approximately 100 million surgical procedures are performed in the US each year (Cullen et al, 2009). Of these, approximately 60% are conducted in an ambulatory setting (Cullen et al, 2009) with up to 80% of patients experiencing pain after their procedure (Apfelbaum et al, 2003; Warfield et al, 1995). Managing acute post-surgical pain is a major challenge for practitioners, given that more 75% of patients report their pain as moderate, severe, or even extreme (Apfelbaum et al, 2003; Gan et al, 2014). In more than half of cases, patients report not receiving adequate pain management following their procedure (Apfelbaum et al, 2003), which raises concerns over the development of chronic pain down the line.

Adequate treatment of acute pain improves clinical and economic outcomes (Apfelbaum et al, 2003) and, during the past two decades, there has been increased focus on the need for better post-surgical pain management. Post-surgical pain is usually managed with multiple pain-reducing medications. The appropriate type, delivery and dose of medications depends on the type of surgery and expected recovery, as well as the patient's own needs.

Potential pain medications include:

- Opioids,
- Local anesthetics,
- NSAIDs,
- Other nonopioid pain relievers, and
- Other psychoactive drugs.

TLC590 is a sustained release delivery technology for the common anesthetic ropivacaine. Ropivacaine is FDA-approved for surgical anesthesia and acute pain management. Ropivacaine is a long-acting amide local anesthetic. It exhibits a similar mechanism of action (MOA) to other local anesthetics in that it reversibly inhibits sodium ion influx in nerve fibers. Amides preferentially bind and inactivate sodium channels in the open state—thereby blocking propagation of action potentials. The dose-dependent inhibition of potassium channels potentiates this action (George et al, 2019).

Ropivacaine has a few properties that make it unique. Ropivacaine is less lipophilic than other local anesthetics, such as bupivacaine, and is less likely to penetrate large myelinated motor fibers. It therefore selectively acts on the nociceptive A, B, and C fibers over the AB (motor) fibers. Ropivacaine is also manufactured as a pure S(-) enantiomer; the S(-) enantiomer has significantly less cardiotoxicity and neurotoxicity (Aberg, 1972; Graf et al, 2002).

3.2.2 Clinical Trials

TLC has studied the clinical effects of TLC590 in one clinical trial (NCT03591146) so far and has an additional clinical trial planned (NCT03838133) (Table 10). The designs of these trials have been outlined in the sections below and where available trial results have been provided.

Table 10 Clinical Program TLC590

Clinical Trial Number	Status	Results
NCT03591146	Completed	Available
NCT03838133	Active Not Recruiting	Not Applicable

3.2.2.1 NCT03591146

Clinical trial NCT03591146 was a phase 1/2, randomized, double-blind, comparator-controlled, dose-escalation study to assess the safety, pharmacokinetics (PK), and efficacy of a single post-surgical application of TLC590 compared with Naropin® (ropivacaine hydrochloride 0.5%) via a single infiltrative local administration in adult patients following inguinal hernia repair surgery. A brief outline of the study can be found in Table 11.

Table 11 NCT03591146 Clinical Trial Design

NCT03591146	
Title	A Phase I/II, Randomized, Double-blind, Comparator-controlled, Dose-escalation Study to Evaluate the Safety, Pharmacokinetics, and Efficacy of TLC590 for Postsurgical Pain Management Following Inguinal Hernia Repair
Type	Interventional
Phase	Phase 1 Phase 2
Design	• Allocation: Randomized • Intervention Model: Sequential Assignment • Intervention Model Description: Subjects will be enrolled in each cohort in a 3:1 ratio. Each cohort will comprise subjects receiving a dose of TLC590 and active comparator drug (Naropin 150 mg) in accordance with the randomization schedule and dose-escalation scheme. Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) • Masking Description: To maintain objectiveness, the study drug will be managed and administered by an independent unblinded team. Subjects, investigators, and all other site staff who directly interact with subjects, evaluate safety and efficacy, and collect subject data, will remain blinded and must not communicate or discuss any study information with the unblinded team. • Primary Purpose: Supportive care
Condition	Inguinal Hernia
Intervention	• Drug: TLC590 TLC590 lyophilized cake will be reconstituted with the TLC590 reconstitution solution to form the TLC590 ropivacaine liposome injectable suspension Other Name: TLC590 (Ropivacaine Liposome Injectable Suspension) • Drug: Naropin Local infiltration of Naropin to produce anesthesia for surgery and analgesia in postoperative pain management. Naropin 150mg [0.5%, 5 mg/mL] x 30 mL Other Name: Naropin, 0.5% Injectable Solution

NCT03591146	
Arms	• Experimental: TLC590 TLC590 (Ropivacaine Liposome Injectable Suspension) is a sustained-release liposome formulation of ropivacaine, white aqueous suspension with ropivacaine concentration at approximately 19 mg/mL. Intervention: Drug: TLC590 • Active Comparator: Naropin Naronpin injection contains ropivacaine HCl. Strength: 150 mg/ 30 mL (5 mg/mL) Size: 30 mL fill, in a 30 mL single dose vial Intervention: Drug: Naropin
Primary Outcome	• Safety and tolerability: Number of SAEs and treatment-related severe AEs [Time Frame: Screening till 30 days post IP administration] Number of SAEs and treatment-related severe AEs
Secondary Outcomes	• Pain intensity assessed using an 11-point NPRS ranging [Time Frame: Baseline till 168 hours post IP administration 11-point NPRS ranging from a score of 0 to 10 • Patient Global Assessment of the method of pain control [Time Frame: 24 hours post IP administration till 168 hours post IP administration] Patient Global Assessment: poor, fair, good, or excellent • AUC of NPRS [Time Frame: For time periods 0-12, 0-24, 0-36, 0-48, 0-72, and 0-96 hours] AUC of NPRS for time periods 0-12, 0-24, 0-36, 0-48, 0-72, and 0-96 hours • Cumulative proportion of pain-free subjects at scheduled timepoints [Time Frame: Baseline till 168 hours post IP administration] Pain-free defined as an NPRS of 0 or 1 • Proportion of pain-free subjects at scheduled timepoints. [Time Frame: Baseline till 168 hours post IP administration] Pain-free defined as an NPRS of 0 or 1 • Cumulative proportion of subjects who used no rescue analgesia [Time Frame: Baseline till 30 days post IP administration] Cumulative proportion of subjects who used no rescue analgesic through 12, 24, 36, 48, 72, and 96 hours • Time to the first postoperative use of rescue analgesics. Total postoperative consumption of rescue analgesics through 12, 24, 36, 48, 72, and 96 hours [Time Frame: Baseline till 30 days post IP administration] Time to the first postoperative use of rescue analgesics. Total postoperative consumption of rescue analgesics through 12, 24, 36, 48, 72, and 96 hours • Average daily rescue analgesic consumption [Time Frame: Baseline till 30 days post IP administration] Average daily rescue analgesic consumption through 24, 48, 72 and 96 hours • Integrated analgesic score using NPRS score and rescue analgesic consumption [Time Frame: Baseline till 30 days post IP administration] Integrated analgesic score using NPRS score and rescue analgesic consumption • Cumulative proportion of subjects who used no postoperative antiemetic therapy [Time Frame: Baseline till 30 days post IP administration] Cumulative proportion of subjects who used no postoperative antiemetic therapy through 12, 24, 36, 48, 72, and 96 hours • Incidence of all adverse events by severity and relatedness [Time Frame: Screening till 30 days post IP administration] Incidence of all adverse events by severity and relatedness • Exposure-response relationship between PK parameters and NPRS scores [Time Frame: Baseline till 168 hours post IP administration] Exposure-response relationship between PK parameters and NPRS scores

NCT03591146	
Enrollment	64
Location	United States
Status	Completed
Sponsor	Taiwan Liposome Company
Investigator	Study Director: Carl Brown, PhD Taiwan Liposome Company
AE = Adverse Event; AUC = Area Under the Concentration Curve; NRPS = Numerical Pain Rating Scale; PK = Pharmacokinetics; SAE = Serious Adverse Event.	

Clinical trial NCT03591146 is a first-in-human trial of 64 adult subjects enrolled in four escalating-dose cohorts with TLC590 190 mg (10 mL), 380 mg (20 mL), 475 mg (25 mL) and 570 mg (30 mL). Each cohort randomized 12 subjects treated with TLC590 and four with Naropin 150 mg (30 mL) via infiltrative local administration following inguinal hernia repair surgery.

Demographic information from the study can be found in Table 12.

Table 12 Demographic Information from Clinical Trial NCT03591146

		Naropin 150 mg (n=16)	TLC590 190 mg (n=12)	TLC590 380 mg (n=12)	TLC590 475 mg (n=12)	TLC590 570 mg (n=12)
Age (years)	Mean (SD)	42.8 (13.68)	50.8 (9.11)	46.5 (13.45)	50.0 (13.05)	44.7 (15.74)
	Median	43.5	55.0	50.0	56.0	48.0
	Min, Max	20, 64	33, 60	20, 62	25, 62	23, 63
Gender n (%)	Male	15 (93.8)	12 (100)	11 (91.7)	10 (83.3)	12 (100)
	Female	1 (6.3)	0	1 (8.3)	2 (16.7)	0
Race n (%)	Asian	0	0	0	0	0
	White	16 (100)	11 (91.7)	12 (100)	12 (100)	12 (100)
	American Indian, Alaska Naive	0	1 (8.3)	0	0	0
Ethnicity n (%)	Hispanic or Latino	1 (6.3)	0	0	0	0
	Non-Hispanic or Latino	15 (93.8)	12 (100)	12 (100)	12 (100)	12 (100)
Min = Minimum; Max = Maximum; SD = Standard Deviation						

(Yeh, Corporate Presentation)

Safety

No serious AEs or local anesthetic system toxicity (LAST) events were observed in the study. TEAEs were mild to moderate in severity and resolved without sequelae (Table 13). Overall, safety and tolerability in all four TLC590 dose groups were similar to the Naropin 150 mg group.

Table 13 Summary of TEAEs in the Safety Population

	Naropin 150 mg (n=16)	TLC590 190 mg (n=12)	TLC590 380 mg (n=12)	TLC590 475 mg (n=12)	TLC590 570 mg (n=12)
Any TEAE n (%)	13 (81.3)	11 (91.7)	8 (66.7)	10 (83.3)	7 (58.3)
Any Related TEAE n (%)	2 (12.5)	1 (8.3)	2 (16.7)	2 (16.7)	2 (16.7)
Subjects with at least one severe TEAE	0	0	0	0	0
Any TEAE of Special Interest	0	0	0	0	0
Ant TEAE Leading to Withdrawal	0	0	0	0	0
TEAE = Treatment Emergent Adverse Event					

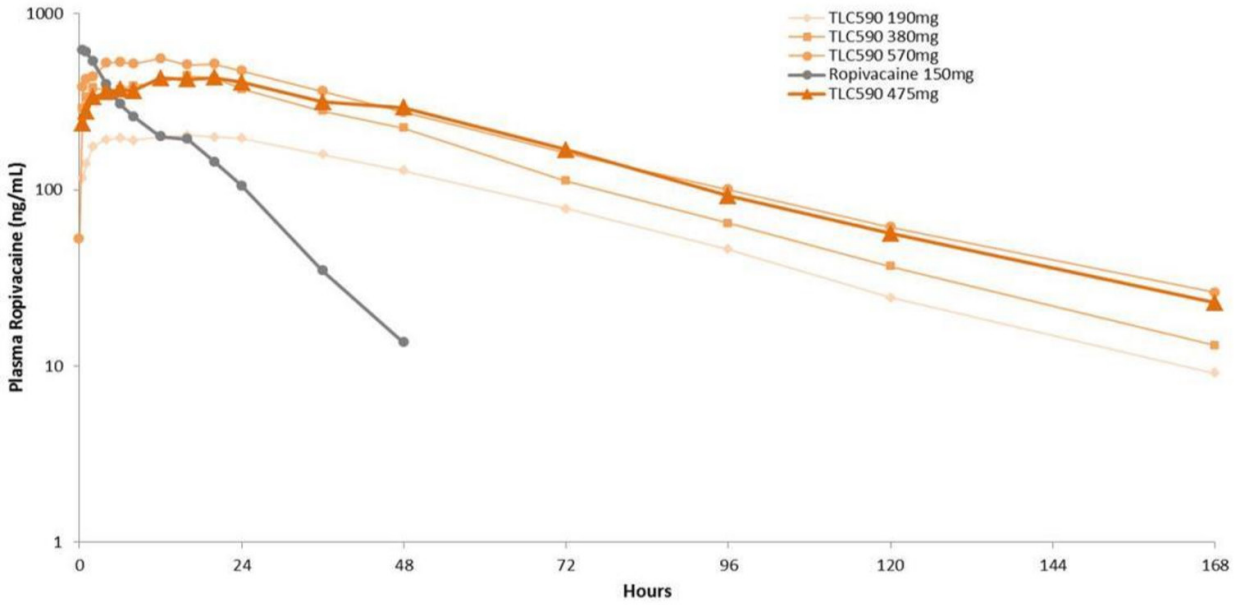
(Bertoch et al, 2019)

The most frequently reported TEAE was nausea (TLC590 groups: 27.1%; Naropin group: 43.8%) followed by constipation (TLC590 groups: 14.6%; Naropin group: 50.0%), and vomiting (TLC590 groups: 12.5%; Naropin group: 31.3%). The incidence of these probable opioid-related events was lower in each TLC590 dose group compared to the Naropin group (Yeh, Corporate Presentation).

Pharmacokinetics

Mean plasma concentrations for TLC590 doses remained at plateau for around 24 hours and declined with an observed half-life significantly longer than the Naropin group (Figure 8).

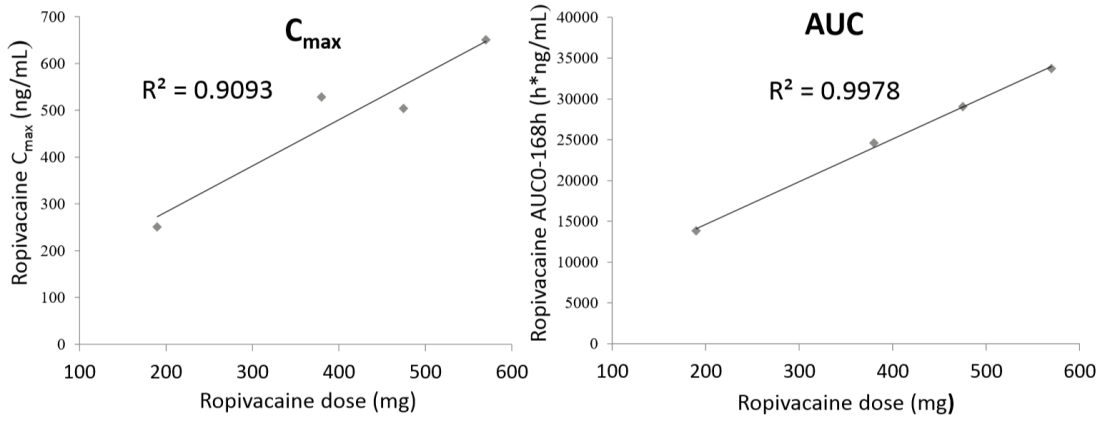
Figure 8 Plasma Naropin Pharmacokinetics Profile



(Bertoch et al, 2019)

TLC590 exhibited highly dose-linear PK in Cmax and AUC (Figure 9). Importantly, all doses of TLC590 had a lower Cmax than that of the Naropin 150 mg group, suggesting decreased potential for LAST. Even at almost four times the dose of Naropin in the comparator group, the Cmax of TLC590 570 mg was still lower than that of the Naropin 150 mg group (Bertoch et al, 2019).

Figure 9 Dose-linear Relationship of Cmax and AUC



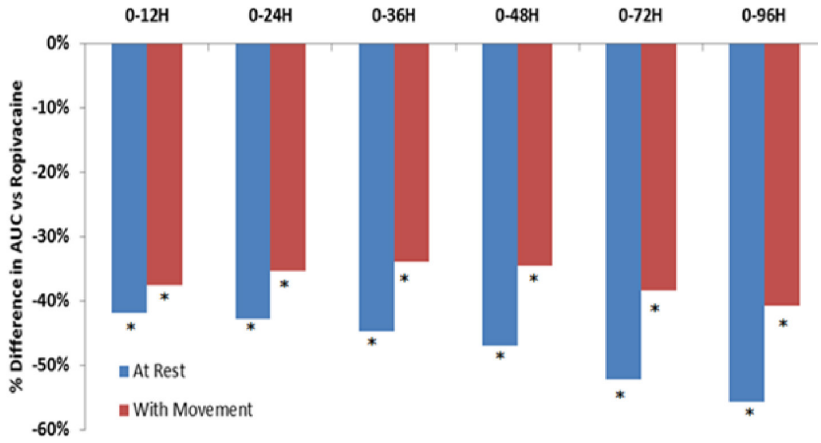
(Bertoch et al, 2019)

Efficacy

The least squares (LS) mean (±SE) AUC of NPRS at rest and with movement in all TLC590 groups were lower than Naropin 150 mg for all time periods, except for the TLC590 190 mg group for 0–12 hours. TLC590 475 mg had statistically significantly lower pain than Naropin 150 mg for all time periods (p-values ranged from 0.0050 to 0.0131). The volume injected at 190 mg dose level was very small and thus complete infiltration of the wound was probably not achieved.

All four doses of TLC590 had reduced post-surgical pain relative to Naropin 150 mg group, as measured by LS mean AUC for NPRS with movement and at rest. For the TLC590 475 mg group there were durable, statistically significant and clinically meaningful reductions in pain intensity with movement and at rest over time (Figure 10) compared to Naropin 150 mg (all $p<0.05$; highest p-value of 0.0131).

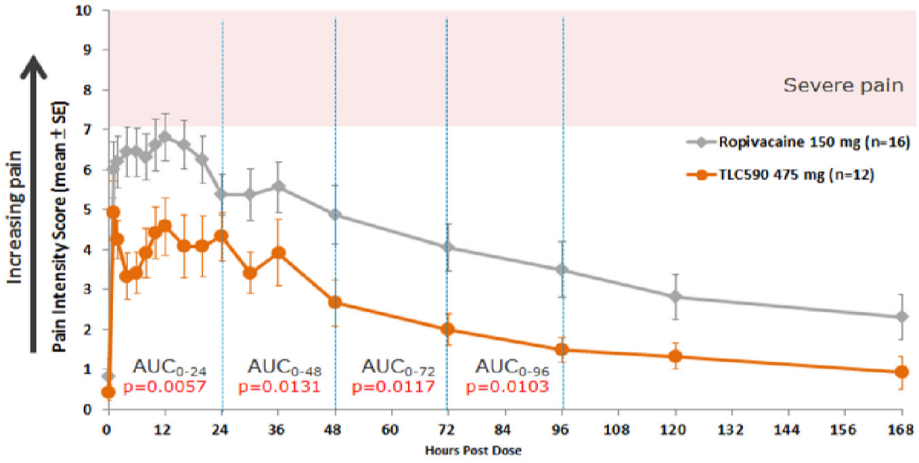
Figure 10 Percent Difference in LS Mean AUC of NPRS at Rest and with Movement for TLC590 475 mg vs Naropin by Time Interval



(Bertoch et al, 2019)

Reduced pain vs. Naropin was maintained through 168 hours (Figure 11).

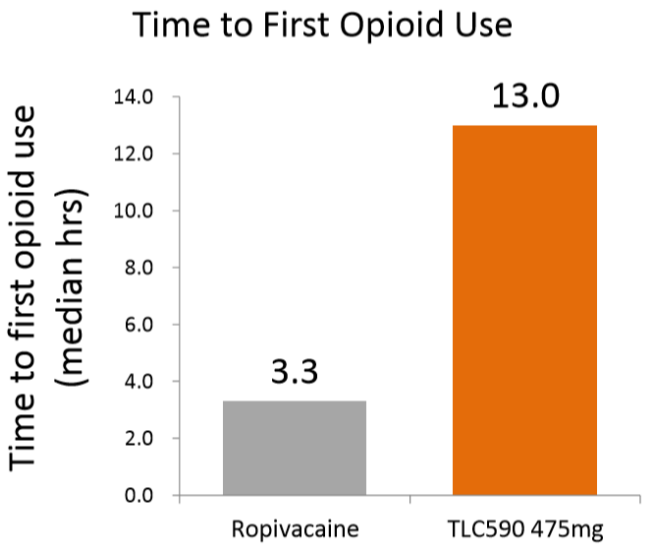
Figure 11 LS Mean (SE) Pain and Movement TLC590



(Bertoch et al 2019)

Median time to first rescue analgesic was 3.2 times longer for TLC590 475 mg than Naropin 150 group (42 hours vs 13 hours). The majority (58.3%) of TLC590 475 mg treated patients did not use any rescue opioids throughout the study. Among those who did use rescue opioid, the median time to first post-surgical opioid use was about four times longer than that of the Naropin 150 group (13.0 hours vs 3.3 hours) (Figure 12).

Figure 12 Time to First Opioid Use Naropin 150 mg vs TLC590 475 mg



(Bertoch et al, 2019)

The mean total opioid consumption in the TLC590 475 mg group was 54% less than that of the Naropin 150 group through 96 hours post-surgery (Table 14).

Table 14 Mean Rescue Opioid Use Over Time (mg/subject) Naropin 150 mg vs TLC590 475 mg

	Naropin	TLC590 475 mg
0-24 hours	78.1	29.2
0-48 hours	115.6	54.2
0-72 hours	118.8	54.2
0-96 hours	118.8	54.2

(Bertoch et al, 2019)

In conclusion, TLC590 showed similar safety and tolerability as the approved drug Naropin with no LAST events and yielded more immediate and long-lasting pain reduction, reducing or eliminating the need for opioids. Patients receiving TLC590 475 mg showed superiority to a clinically relevant dose of Naropin, with lower mean pain at all points and significantly reduced total pain at time intervals through four days after surgery.

3.2.2.2 NCT03838133

Clinical trial NCT03838133 is an ongoing phase 2, randomized, double-blind, comparator- and placebo-controlled study to evaluate the safety, PK, and efficacy of TLC590 compared with Naropin and placebo via a single infiltrative local administration in adult subjects following bunionectomy. A brief outline of the study can be found in Table 15.

Table 15 NCT03838133 Clinical Trial Design

NCT03838133	
Title	A Phase 2, Randomized, Double-blind, Comparator- and Placebo-controlled Study to Evaluate the Safety, Pharmacokinetics, and Efficacy of TLC590 for Postsurgical Pain Management Following Bunionectomy
Type	Interventional
Phase	Phase 2
Design	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) Primary Purpose: Supportive Care
Condition	Hallux Valgus
Intervention	• Drug: TLC590 TLC590 lyophilized cake will be reconstituted with the TLC590 reconstitution solution to form the TLC590 ropivacaine liposome injectable suspension Other Name: TLC590 (Ropivacaine Liposome Injectable Suspension) • Drug: Naropin Local infiltration of Naropin to produce anesthesia for surgery and analgesia in postoperative pain management. 50 mg (0.5%, 10 mL) Other Name: Naropin, 0.5% Injectable Solution • Drug: Normal Saline Normal Saline (0.9% sodium chloride, 10ml) Other Name: Saline
Arms	• Experimental: TLC590 dose 1 TLC590 (Ropivacaine Liposome Injectable Suspension) is a sustained-release liposome formulation of ropivacaine, white aqueous suspension with ropivacaine concentration at approximately 19 mg/mL. Intervention: Drug: TLC590 • Experimental: TLC590 dose 2 TLC590 (Ropivacaine Liposome Injectable Suspension) is a sustained-release liposome formulation of ropivacaine, white aqueous suspension with ropivacaine concentration at approximately 19 mg/mL. Intervention: Drug: TLC590 • Experimental: TLC590 dose 3 TLC590 (Ropivacaine Liposome Injectable Suspension) is a sustained-release liposome formulation of ropivacaine, white aqueous suspension with ropivacaine concentration at approximately 19 mg/mL. Intervention: Drug: TLC590 • Active Comparator: Naropin Naronpin injection contains ropivacaine HCl. 50 mg (0.5%, 10 mL) Intervention: Drug: Naropin • Placebo Comparator: Placebo Normal Saline (0.9% sodium chloride, 10 mL) Intervention: Drug: Normal Saline
Primary Outcome	• AUC of numerical pain rating scale [Time Frame: 0-24 hours, 0-72 hours] AUC of the numerical pain rating scale (NPRS-R) following bunionectomy surgery

NCT03838133	
Secondary Outcomes	• PK Cmax [Time Frame: 0-168 hours] Maximum blood concentration (Cmax) • PK Tmax [Time Frame: 0-168 hours] Time to reach maximum blood concentration (Tmax) • PK t½ [Time Frame: 0-168 hours] Terminal elimination half-life (t½) • PK AUC [Time Frame: 0-24, 0-48 , 0-72, 0-96 hours] Area under the blood concentration-time curve (AUC) • Number of treatment-emergent adverse event (TEAE) [Time Frame: Screening through Day 43] Number of treatment-emergent adverse event (TEAE) occurred in the study • Electrocardiogram (RR interval, QRS duration, QT duration, PR duration, QTcF interval) [Time Frame: Screening through Day 43] The 12-lead electrocardiogram (ECG) result will be assessed including RR interval, QRS duration, QT duration, PR duration, and QTcF interval • Wound assessment by Numerical Pain Rating Scale (NPRS) [Time Frame: Day 1 through Day 43] The surgical site will be examined by the investigator using a 5-point numerical pain rating scale as follows: o Normal healing o Bruising, erythema, edema o Clear or hemoserous drainage o Evidence of cellulitis such as heat, spreading erythema, purulent discharge Tissue breakdown, wound dehiscence, hematoma requiring aspiration • AUC of NPRS-R (0-10) [Time Frame: 0-36, 0-48, 0-72, 0-96, 0-120,24-48, 48-72, 72-96, 96-120, and 120-168 hours] AUC of NPRS-R (0-10) • Proportion of pain-free (NPRS-R of 0 or 1) subjects [Time Frame: at 12, 24, 36, 48, 72, 96, 120, and 168 hours] Proportion of pain-free (NPRS-R of 0 or 1) subjects • Proportion of subjects who used no rescue opioid analgesic [Time Frame: through 12, 24, 36, 48, 72, 96, 120, and 168 hours] Proportion of subjects who used no rescue opioid analgesic • Time to the first postoperative use of rescue opioid analgesics [Time Frame: Day 1 to Day 43] Time to the first postoperative use of rescue opioid analgesics • Total postoperative consumption of rescue opioid analgesics used [Time Frame: through 24, 36, 48, 60, 72, 96, 120, and 168 hours] Total postoperative consumption of rescue opioid analgesics used
Enrollment	223
Location	United States
Status	Active, not recruiting
Sponsor	Taiwan Liposome Company
Investigator	Study Director: Carl Brown, PhD Taiwan Liposome Company
AUC = Area Under the Concentration Curve; Cmax = Maximum Concentration; ECG = Electrocardiogram; NPRS = Numerical Pain Rating Scale; PK = Pharmacokinetics; t½ = Half-life; TEAE = Treatment-emergent Adverse Event; Tmax = Time to Maximum Concentration	

TLC has announced initial results from the analysis of Part 1 of the TLC590 phase 2 clinical trial for post-surgical pain management following bunionectomy (TLC Press Release, June 14, 2019). The key findings from the analysis were as follows:

- Dose linearity and relative bioavailability of TLC590 have been established.
- All three doses of TLC590 were well tolerated, with a safety profile comparable to Naropin.
    - Most treatment-emergent adverse events were mild to moderate in severity.
    - There were no treatment-related or serious AEs, and no AEs leading to withdrawal.

The TLC590 228 mg dose was chosen to move forward within Part 2 based on the maximum feasible volume for bunionectomy. TLC also changed the active comparator arm from Naropin to bupivicaine for Part 2 of the study.

3.3 TLC399

3.3.1 Background

TLC is currently developing TLC399 as an intravitreal injection for the treatment of macular edema due to retinal vein occlusion (RVO). Macular edema with RVO is a disease of the retina that causes impaired vision, characterized by leakage of fluid from the blood vessels in the retina. RVO is caused by thrombosis in the central (CRVO) or branch (BRVO) retinal veins (Green et al, 1981).

Worldwide, it is estimated that 16.4 million people have had an RVO, 13.9 million with BRVO and 2.5 million with CRVO (Sophie et al, 2013). There are approximately 180,000 new RVOs in the US each year: 150,000 BRVOs and 30,000 CRVOs (Klein et al, 2008).

The following conditions have been associated RVOs:
- Systemic hypertension,
- Diabetes mellitus,
- Hyperlipidemia,
- Hyper-homocysteinemia,
- Blood coagulation disorders,
- Systemic inflammatory disorders,
- Glaucoma,
- Short axial length, and
- High body mass index.

(Bertelsen et al, 2014; Elman et al, 1990; Dodson et al, 1982; Koizumi et al, 2007; Wang et al, 2014)
Current therapies for macular edema due to RVO include:

- Laser Photocoagulation
- Anti-vascular Endothelial Growth Factor Therapy
- Intraocular Steroids
    - Triamcinolone Acetonide
    - Dexamethasone Implant

Lashey et al, 2019 did a systematic review and meta-analysis of intravitreal medications for RVO. When dexamethasone implant was compared with sham treatment in RVO eyes (GENEVA study) (Haller et al, 2010; Haller et al, 2011; Guignier et al, 2013), it was found that after three months of treatment, both structural and functional improvements were significantly higher in eyes treated with dexamethasone implant compared to sham injection, but this effect was not maintained after six months. The maximum therapeutic effect of intravitreal dexamethasone implant is about 12 weeks after injection. Therefore, treatment repetition is necessary even with dexamethasone implantable agents.

TLC399 applies sustained release technology for the treatment of macular edema secondary to RVO. It's designed to provide benefits for a much longer duration than existing therapies and thus should reduce administration frequency.

3.3.2 Clinical Trials

TLC has so far studied the clinical effects of TLC399 in one clinical trial (NCT02006147) and an additional clinical trial is planned (NCT03093701) (Table 16). The designs of these trials have been outlined in the sections below and where available trial results have been provided.

Table 16 Clinical Program TLC399

Clinical Trial Number	Status	Results
NCT02006147	Recruiting	Not Applicable
NCT03093701	Active, Not Recruiting	Not Applicable

3.3.2.1 NCT02006147

Clinical trial NCT02006147 is a phase 1/2 trial to determine whether TLC399 provides an ideal, safe, long-acting, dexamethasone sodium phosphate delivery system for the treatment of macular edema due to RVO. The trial consists of two parts:

- Part 1 of this study is the open-label, sequential dose escalation portion to determine dose limiting toxicity (DLT) of TLC399 in patients with macular edema due to CRVO or BRVO. The safety results will be evaluated by the Safety Monitor Committee (SMC) regularly every 6 months and after the last patient of each cohort completes the DLT observation period. The SMC will advise or give permission for further dose escalation, de-escalation, or any study design adjustments. After the study drug administration, patients will continue to be evaluated for efficacy and safety outcomes up to a period of 12 months unless the patient is withdrawn or discontinues the study.
    - Group R1: 0.24 mg DSP with 100 mM PL (20 µL)
    - Group 1: 0.36 mg DSP with 100 mM PL (30 µL)
    - Group 2: 0.6 mg DSP with 100 mM PL (50 µL)
    - Group 3: 0.6 mg DSP with 50 mM PL (50 µL)
- Part 2 of this study is the open-label, single-arm design portion to investigate the use of TLC399 in patients with macular edema due to CRVO or BRVO at the dose level selected from Part 1. The enrollment of subjects for analysis will include approximately 20 patients, inclusive of Parts 1 and 2 for the selected dose group. The safety and efficacy outcomes will be assessed for up to 12 months.

A brief outline of the study can be found in Table 17.

Table 17 NCT02006147 Clinical Trial Design

NCT02006147	
Title	Phase I/II Trial of TLC399 (ProDex) in Patients with Macular Edema Due to Retinal Vein Occlusion (RVO)
Type	Interventional
Phase	Phase 1 Phase 2
Design	• Intervention Model: Single Group Assignment • Masking: None (Open Label) • Primary Purpose: Treatment
Condition	• Central Retinal Vein Occlusion with Macular Edema • Branch Retinal Vein Occlusion with Macular Edema

NCT02006147	
Intervention	Drug: TLC399 Dose-escalation Study from 100 mM PL (20 µL) with 0.24 mg DSP to 100 mM PL (20 µL) with 0.36 mg DSP to 100 mM PL (20 µL) with 0.6 mg DSP to 50 mM PL (10 µL) with 0.6 mg DSP.
Arms	Experimental: TLC399 TLC399 is manufactured with the proprietary lipid formulation in lyophilized form (BioSeizer) for the reconstitution with the aqueous DSP. Intervention: Drug: TLC399
Primary Outcome	Part 1: Dose-limiting Toxicity (DLT) [Time Frame: 4 weeks] Ocular AEs Part 2: Safety Assessment: Number of SAEs and treatment-related severe AEs [Time Frame: Up to 1 year] Number of SAEs and treatment-related severe AEs
Secondary Outcomes	• Part 1: Safety Assessment: Number of SAEs and treatment-related severe AEs [Time Frame: Up to 1 year] Number of SAEs and treatment-related severe AEs • Part 2: Mean change of intraocular pressure (IOP) [Time Frame: at day 1, week 1, month 1, month 2, month 3, month 4, month 5, month6, month 7.5, month 9, month 10.5, and month 12] Mean change from baseline in IOP in the study eye • Part 2: Mean change of letters read correctly (BCVA) [Time Frame: at day 1, week 1, month 1, month 2, month 3, month 4, month 5, month 6, month 7.5, month 9, month 10.5, and month 12] Mean change from baseline in BCVA in the study eye • Part 2: Mean change of retinal thickness (OCT) [Time Frame: at day 1, week 1, month 1, month 2, month 3, month 4, month 5, month 6, month 7.5, month 9, month 10.5, and month 12] Mean change from baseline of OCT in the study eye • Part 2: Gain in best BCVA [Time Frame: at day 1, week 1, month 1, month 2, month 3, month 4, month 5, month 6, month 7.5, month 9, month 10.5, and month 12] Proportion of patients with BCVA gain of 15 or more letters from baseline in the study eye • Time to achieve best BCVA [Time Frame: up to 12 months] Time to achieve a treatment response of gain of 15 or more letters from baseline BCVA in the study eye
Enrollment	30
Location	Taiwan
Status	Recruiting
Sponsor	Taiwan Liposome Company
Investigator	Study Director: Carl Brown, PhD Taiwan Liposome Company

AE = Adverse Event; BVCA = Branch Retinal Vein Occlusion; DLT = Dose-limiting Toxicity; DSP = Dexamethasone Sodium Phosphate; IOP = Intraocular Pressure; OCT = Change Retinal Thickness; ProDex = TLC399; PL = Phospholipids; RVO = Retinal Vein Occlusion; SAE = Serious Adverse Event

TLC has stated that this phase 1/2 safety trial has demonstrated encouraging signs of efficacy in both the reduction of retinal central subfield thickness and improvements in visual acuity. However, no further results are publicly available at this time.

3.3.2.2 NCT03093701

Clinical trial NCT03093701 is a phase 2, randomized, double-masked trial designed to investigate the use of TLC399 in subjects with macular edema due to CRVO or BRVO. A brief outline of the study can be found in Table 18.

Table 18 NCT03093701 Clinical Trial Design

NCT03093701	
Title	TLC399 (ProDex) in Subjects with Macular Edema Due to Retinal Vein Occlusion (RVO)
Type	Interventional
Phase	Phase 2
Design	• Allocation: Randomized • Intervention Model: Parallel Assignment • Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) • Primary Purpose: Treatment
Condition	• Retinal Vein Occlusion • Macula Edema
Intervention	Drug: TLC399 (ProDex) 2-vial system: TLC399-DSP and TLC399-Lipid Other Name: TLC399
Arms	• Experimental: Group 1 TLC399 (ProDex) 0.36mg DSP with 100 mM PL Intervention: Drug: TLC399 (ProDex) • Experimental: Group 2 TLC399 (ProDex) 0.6 mg DSP with 100 mM PL Intervention: Drug: TLC399 (ProDex) • Experimental: Group 3 TLC399 (ProDex) 0.6 mg DSP with 50 mM PL Intervention: Drug: TLC399 (ProDex) • Experimental: Group 4 TLC399 (ProDex) 0.84 mg DSP with 50 mM PL Intervention: Drug: TLC399 (ProDex)
Primary Outcome	BCVA score [Time Frame: 6 months after dosing] Proportion of subjects with BCVA gain of 15 or more letters from baseline in the study eye
Secondary Outcomes	Not Provided
Enrollment	61
Location	United States
Status	Active, not recruiting

NCT03093701	
Sponsor	Taiwan Liposome Company
Investigator	Study Director: Yvonne Shih Taiwan Liposome Company, Ltd.
DSP = Dexamethasone Sodium Phosphate; PL = Phospholipids; ProDex = TLC399; RVO = Retinal Vein Occlusion	

This randomized, double-blind, dose finding phase 2 trial is underway. No further results are publicly available at this time.

3.4 TLC178

3.4.1 Background

TLC178 is a proprietary NanoX formulation of the anticancer drug vinorelbine, developed for the treatment of rhabdomyosarcoma (RMS). RMS is the most common soft tissue sarcoma accounting for 5–8% of malignant tumors in children and adolescents. Children with high risk disease have poor prognosis. Anti-RMS therapies include surgery, radiation and combination chemotherapy.

TLC is developing TLC178 for treatment of pediatric RMS. The increased specificity of TLC178 for tumor versus non-tumor tissue through the use of the NanoX technology has enhanced permeability and retention effects. This should enable greater dose intensity, with attendant benefits in antitumor response without impairing the safety profile. TLC178 is predicted to have significantly lower myelosuppression, resulting in a lower rate of severe neutropenia.

In parallel with the pediatric RMS study, TLC plans to conduct a series of trials evaluating TLC178 in soft tissue sarcoma (STS) and other indications for which vinorelbine has been approved, such as non-small cell lung carcinoma (NSCLC).

3.4.2 Clinical Trial

3.4.2.1 NCT02925000

Clinical trial NCT02925000 is a phase 1/2a, open label, dose-escalation study investigating the safety, tolerability, and PK of intravenous (IV) liposomal Vinorelbine Tartrate Injection in patients with advanced malignancy. A brief outline of the study can be found in Table 19.

Table 19 NCT02925000 Clinical Trial Design

NCT02925000	
Title	A Phase I/IIa, Open Label, Dose-escalation Study Investigating the Safety, Tolerability, and Pharmacokinetics of Intravenous Liposomal Vinorelbine Tartrate Injection in Patients with Advanced Malignancy
Type	Interventional
Phase	Phase 1 Phase 2
Design	• Intervention Model: Single Group Assignment • Masking: None (Open Label) • Primary Purpose: Treatment
Condition	Cancer
Intervention	Interventional
Arms	Phase 1 Phase 2
Primary Outcome	Maximum tolerated dose (MTD) determination [Time Frame: 4 weeks] To determine the maximum tolerated dose (MTD) and recommended phase II dose (RP2D) of intravenous LipoVNB given every 4 weeks (Q4W) in patients with advanced malignancies.

NCT02925000	
Secondary Outcomes	• Pharmacokinetics (PK) parameters of AUC (0-inf) calculated by plasma concentration of vinorelbine [Time Frame: from day 1 to day 29] Area under the plasma concentration time curve from zero (predose) extrapolated to infinity • Pharmacokinetics (PK) parameters of AUC (0-inf) calculated by plasma concentration of major metabolite, 4-O-deacetylvinorelbine [Time Frame: from day 1 to day 29] Area under the plasma concentration time curve from zero (predose) extrapolated to infinity • Pharmacokinetics (PK) parameters of AUC (0 - last) calculated by plasma concentration of vinorelbine [Time Frame: from day 1 to day 29] Area under the plasma concentration time curve from zero (predose) to the time of the last quantifiable concentration • Pharmacokinetics (PK) parameters of AUC (0 - last) calculated by plasma concentration of major metabolite, 4-O-deacetylvinorelbine [Time Frame: from day 1 to day 29] Area under the plasma concentration time curve from zero (predose) to the time of the last quantifiable concentration • Pharmacokinetics (PK) parameters of Cmax calculated by plasma concentration of vinorelbine [Time Frame: from day 1 to day 29] Maximum plasma concentration observed • Pharmacokinetics (PK) parameters of Cmax calculated by plasma concentration of major metabolite, 4-O-deacetylvinorelbine [Time Frame: from day 1 to day 29] Maximum plasma concentration observed • Pharmacokinetics (PK) parameters of Tmax calculated by plasma concentration of vinorelbine [Time Frame: from day 1 to day 29] Time of Cmax • Pharmacokinetics (PK) parameters of Tmax calculated by plasma concentration of major metabolite, 4-O-deacetylvinorelbine [Time Frame: from day 1 to day 29] Time of Cmax • Pharmacokinetics (PK) parameters of t½ calculated by plasma concentration of vinorelbine [Time Frame: from day 1 to day 29] Apparent terminal half life • Pharmacokinetics (PK) parameters of t½ calculated by plasma concentration of 4-O-deacetylvinorelbine [Time Frame: from day 1 to day 29]
Enrollment	51

NCT02925000	
Location	Taiwan United States
Status	Recruiting
Sponsor	Taiwan Liposome Company
Investigator	Study Director: Karen Chen Taiwan Liposome Company
AE = Adverse Event; AUC = Area Under the Concentration Curve; Cmax = Maximum Concentration; CTCAE = Common Terminology Criteria for Adverse Events; MRT = Mean Residence Time; MTD = Maximum Tolerated Dose; PFS = Progression Free Survival; PK = Pharmacokinetics; Q4W = Every Four Weeks; RP2D = Recommended Phase II Dose; t½ = Half Life; TEAE = Treatment Emergent Half Life; Tmax = Time to Maximum Concentration	

This trial is currently underway. No results are publicly available at this time.

4 Conclusions

The Taiwan Liposome Company is a clinical-stage specialty pharmaceutical company dedicated to the development and commercialization of best-in-class novel nanomedicines that combine its proprietary lipid-assembled drug delivery platform with approved APIs. TLC currently has four assets, in three program areas, at various stages in development. The program areas include pain management (TLC599, TLC590), ophthalmology (TLC399) and oncology (TLC178).

TLC599

TLC599 is a proprietary BioSeizer formulation that has the potential to enable patients to receive both immediate and sustained benefit from the local delivery of a highly potent and clinically validated steroid that typically has a very short half-life. Potential advantages of this product include:

- Rapid pain relief maintained for up to 24 weeks
- Minimized cartilage damage and toxicity
- Improved drug retention in joint
- Flexibility of needle size to allow for future expanded indications into small joints

TLC590

TLC590 is a proprietary BioSeizer formulation that brings sustained release delivery technology to the common anesthetic ropivacaine, with the goal of reducing the frequency of administration for local anesthesia for post-surgical pain. More effective pain relief may also allow patients to avoid the problems of opioid therapies often used for the treatment of post-surgical pain. Potential advantages of this product include:

- Non-opioid
- Fast, immediate onset of pain relief
- Potential pain relief of up to 168 hours
- Less cardiovascular and central nervous system toxicity
- Reduced frequency of administration
- Proprietary manufacturing process to effectively reduce the cost of production

TLC399

TLC399 is a proprietary BioSeizer formulation of dexamethasone sodium phosphate, intended as an intravitreal, or in-eye, injection for the treatment of macular edema due to retinal vein occlusion. In pre-clinical models TLC399

has been shown to provide therapeutic levels of DSP in the eye for at least six months after a single administration. Potential advantages of this product include:

- Rapid onset
- Designed to achieve prolonged sustained release duration beyond six months
- Smaller administration needle to reduce risk of conjunctival hemorrhaging and infections

TLC178

TLC178 is a proprietary NanoX formulation of the anticancer drug vinorelbine, developed for the treatment of rhabdomyosarcoma, a rare form of soft tissue sarcoma that most frequently occurs in children. Potential advantages of this product include:

- Improved selective delivery to tumor vs non-tumor tissue
- Higher drug concentration at tumor confers higher activity
- Less drug to non-tumor sites to reduce myelosuppression, enabling higher dose frequency
- Efficacy improvement in treatment response rate and duration of response

In conclusion, TLC has extensive experience with liposome science which has allowed them to combine the benefits of fast drug onset speed and extended duration. In addition, their technology has improved API concentrations at target tissues while decreasing unwanted systemic exposures. TLC have used their proprietary technology platforms to assemble a diverse portfolio of product candidates that target significant areas of unmet medical need. Their lead candidate TLC599 is currently being tested in a pivotal phase 3 trial, which if successful is expected to lead to the submission of an NDA with the FDA.

5 References

Aberg G. Toxicological and local anaesthetic effects of optically active isomers of two local anaesthetic compounds. Acta Pharmacol Toxicol (Copenh). 1972;31(4):273-286.

Alghadir AH, Anwer S, Iqbal A, Iqbal ZA. Test-retest reliability, validity, and minimum detectable change of visual analog, numerical rating, and verbal rating scales for measurement of osteoarthritic knee pain. J Pain Res. 201826;11:851-856. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5927184/pdf/jpr-11-851.pdf

Apfelbaum JL, Chen C, Mehta SS, Gan TJ. Postoperative pain experience: Results from a national survey suggest postoperative pain continues to be undermanaged. Anesth Analg. 2003;97:534-540.

Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt L. Validation study of WOMAC: A health status instrument for measuring clinically important patient relevant outcomes following total hip or knee arthroplasty in osteoarthritis. J Orthop Rheumatol. 1988a;1:95-108.

Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: A health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol. 1988b;15:1833-1840.

Bellamy N, Buchanan WW. A preliminary evaluation of the dimensionality and clinical importance of pain and disability in osteoarthritis of the hip and knee. Clin Rheumatol. 1986;5(2):231-241.

Bellamy N. Outcome measurement in osteoarthritis clinical trials. J Rheumatol. 1995;43 Suppl:49-51.
Bertelsen M, Linneberg A, Christoffersen N, Vorum H, Gade E, Larsen M. Mortality in patients with central retinal vein occlusion. Ophthalmology. 2014;121(3):637-642.

Bertoch TM, Brown CO, Wu C-F, Hu P-H, Tai T-T, Jao WYN, Kuo C-Y, Wang H-T, Kuo M-W, Tseng Y-L. A phase 1/2, randomized, double-blind, comparator-controlled, dose-escalation study to evaluate the safety, pharmacokinetics, and efficacy of TLC590 for postsurgical pain management following inguinal hernia repair. https://www.tlcbio.com/upload/media/media/posters/TLC590A1001%20ASA%20poster_Final

Cullen KA, Hall MJ, Golosinskiy A. Ambulatory surgery in the United States, 2006. Natl Health Stat Report. 2009;(11):1-25. https://www.cdc.gov/nchs/data/nhsr/nhsr011.pdf

Dodson PM, Galton DJ, Hamilton AM, Blach RK. Retinal vein occlusion and the prevalence of lipoprotein abnormalities. British Journal of Ophthalmology. 1982;66(3):161-164. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1039744/pdf/brjopthal00171-0025.pdf

Elman MJ, Bhatt AK, Quinlan PM, Enger C. The risk for systemic vascular diseases and mortality in patents with central retinal vein occlusion. Ophthalmology. 1990;97(11):1543-1548.

Felson DT, Anderson JJ, Naimark A, Walker AM, Meenan RF. Obesity and knee osteoarthritis: The Framingham Study. Ann Intern Med. 1988;109:18-24.

Fletcher CD, Bridge JA, Hogendoorn PCW, Mertens F. WHO Classification of Tumours of Soft Tissue and Bone. Lyon, France: International Agency for Research on Cancer; 2013.

Gan TJ, Habib AS, Miller TE, White W, Apfelbaum JL. Incidence, patient satisfaction, and perceptions of postsurgical pain: Results from a US national survey. Curr Med Res Opin. 2014;30:149-160.

Gelber AC, Hochberg MC, Mead LA, Wang N-Y, Wigley FM, Klag MJ. Body mass index in young men and the risk of subsequent knee and hip osteoarthritis. Am J Med. 1999;6:542-548.

George AM, Liu M. Ropivacaine. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019 Oct 17. https://www.ncbi.nlm.nih.gov/books/NBK532924/

Ghouri A, Conaghan PG. Update on novel pharmacological therapies for osteoarthritis. Ther Adv Musculoskelet Dis. 2019;11:S125-S129. https://www.clinexprheumatol.org/article.asp?a=14728

Graf BM, Abraham I, Eberbach N, Kunst G, Stowe DF, Martin E. Differences in cardiotoxicity of bupivacaine and ropivacaine are the result of physicochemical and stereoselective properties. Anesthesiology. 2002;96(6):1427-1434.

Green WR, Chan CC, Hutchins GM, Terry JM. Central retinal vein occlusion: A prospective histopathologic study of 29 eyes in 28 cases. Retina. 1981;1(1):27-55.

Grodzinsky AJ, Wang Y, Kakar S, Vrahas MS, Evans CH. Intra-articular dexamethasone to inhibit the development of post-traumatic osteoarthritis. J Orthop Res. 2017;35:406-411. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5604325/pdf/nihms904590.pdf

Guignier B, Subilia-Guignier A, Fournier I, Ballonzoli L, Speeg-Schatz C, Gaucher D. Prospective pilot study: Efficacy of intravitreal dexamethasone and bevacizumab injections in the treatment of macular oedema associated with branch retinal vein occlusion. Ophthalmologica. 2013;230(1):43-49.

Haller JA, Bandello F, Belfort R, Blumenkranz MS, Gillies M, Heier J, Loewenstein A, Yoon Y, Jacques M, Jiao J, Li X, Whitcup SM. Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion. Ophthalmology. 2010;117(6):1134.e3-1146.e3.

Haller JA, Bandello F, Belfort R, Blumenkranz MS, Gillies M. Heier J, Loewenstein A, Yoon YH, Jiao J, Li X, Whitcup SM. Dexamethasone intravitreal implant in patients with macular edema related to branch or central retinal vein occlusion: twelve-month study results. Ophthalmology. 2011;118(12):2453-2460.

Hjermstad MJ, Fayers PM, Haugen DF, Caraceni A, Hanks GW, Loge JH, Fainsinger R, Aass N, Kaasa S; European Palliative Care Research Collaborative (EPCRC). Studies comparing numerical rating scales, verbal rating scales, and visual analogue scales for assessment of pain intensity in adults: a systematic literature review. J Pain Symptom Manage. 2011;41(6):1073-1093.

Hollander JL. Clinical use of dexamethasone: Role in treatment of patients with arthritis. J Am Med Assoc. 1960;172:306-310.

Huebner KD, Shrive NG, Frank CB. Dexamethasone inhibits inflammation and cartilage damage in a new model of post-traumatic osteoarthritis. J Orthop Res. 2014;32:566-572.

Hunter D, Chang C-C, Wei J-C, Lin H-Y, Brown C, Shih S-F. Single Intra-articular injection of TLC599 provided sustained pain relief through 24 weeks in participants with symptomatic knee osteoarthritis. World Congress of Osteoarthritis. 19-A-87-OARSI. https://www.tlcbio.com/upload/media/media/posters/OARSI2019%20-%20TLC%20Abstract%20SINGLE%20INTRAARTICULAR%20INJECTION%20OF%20TLC599%20PROVIDED%20SUSTAINED%20PAIN%20RELIEF%20THROUGH%2024.pdf

Jensen LK. Hip osteoarthritis: Influence of work with heavy lifting, climbing stairs or ladders, or combining kneeling/squatting with heavy lifting. Occup Environ Med. 2008a;65:6-19.

Jensen LK. Knee osteoarthritis: Influence of work involving heavy lifting, kneeling, climbing stairs or ladders, or kneeling/squatting combined with heavy lifting. Occup Environ Med. 2008b;65:72-89.
Johnson VL, Hunter DJ. The epidemiology of osteoarthritis. Best Pract Res Clin Rheumatol. 2014;28:5-15.

Kaila-kangas L, Arokoski J, Impivaara O, Viikari-juntura E, Leino-arjas P, Luukkone, R, Heliövaara M. Associations of hip osteoarthritis with history of recurrent exposure to manual handling of loads over 20 kg and work participation: A population-based study of men and women. Occup Environ Med. 2011;68:734-738.

Kapoor M, Martel-Pelletier J, Lajeunesse D, Pelletier JP, Fahmi H. Role of proinflammatory cytokines in the pathophysiology of osteoarthritis. Nat Rev Rheumatol. 2011;7:33-42.

Klein R, Moss SE, Meuer SM, Klein BE. The 15-year cumulative incidence of retinal vein occlusion: the Beaver Dam Eye Study. Arch Ophthalmol. 2008;126(4):513-518. https://jamanetwork.com/journals/jamaophthalmology/fullarticle/420392

Koizumi H, Ferrara DC, Bruè C, Spaide RF. Central retinal vein occlusion case-control study. American Journal of Ophthalmology. 2007;144(6):858-863.

Lai C-C, Chiang C-C, Lee CS, Chang C-C, Lin H-Y, Chen T-L, Shih S-F. Safety, tolerability, and efficacy of a novel sustained-release liposomal formulation of dexamethasone sodium phosphate (TLC599) in patients with knee osteoarthritis. 20th Asia Pacific League of Associations for Rheumatology Congress. https://www.ir-cloud.com/taiwan/4152/events/133/EN/aplar%20poster_a6nJ331cfdBJ.pdf

Lashay A, Riazi-Esfahani H, Mirghorbani M, Yaseri M. Intravitreal medications for retinal vein occlusion: Systematic review and meta-analysis. J Ophthalmic Vis Res. 2019;14(3):336-366. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6815330/pdf/jovr-14-336.pdf

Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, Gabriel S, Hirsch R, Hochberg MC, Hunder GG, Jordan JM, Katz JN, Kremers HM, Wolfe F. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. Arthritis Rheum. 2008;58:26-35.

Li Y, Wang Y, Chubinskaya S, Schoeberl B, Florine E, Kopesky P, Grodzinsky AJ. Effects of insulin-like growth factor-1 and dexamethasone on cytokine-challenged cartilage: Relevance to post-traumatic osteoarthritis. Osteoarthritis Cartilage. 2015;23:266-274. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4304966/pdf/nihms641694.pdf

Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohan, H, AlMazroa MA, Amann M, Anderson HR, Andrews, KG. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: A systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380:2224-2260.

Lu YC, Evans CH, Grodzinsky AJ. Effects of short-term glucocorticoid treatment on changes in cartilage matrix degradation and chondrocyte gene expression induced by mechanical injury and inflammatory cytokines. Arthritis Res Ther. 2011;13:R142. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3308070/pdf/ar3456.pdf

Madry H, Luyten FP, Facchini A. Biological aspects of early osteoarthritis. Knee Surg Sports Traumatol Arthrosc. 2012;20:407-422.

Malfait AM, Tortorella M, Thompson J, Hills R, Meyer DM, Jaffee BD, Chinn K, Ghoreishi-Haack N, Markosyan S, Arner EC. Intra-articular injection of tumor necrosis factor-alpha in the rat: An acute and reversible in vivo model of cartilage proteoglycan degradation. Osteoarthritis Cartilage. 2009;17:627-635.

Martel-Pelletier J, Barr AJ, Cicuttini FM, Conaghan PG Cooper C, Goldring MB, Goldring SR, Jones G, Teichtahl AJ, Pelletier J-P, Osteoarthritis. Nat Rev Dis Primers. 2016;2:16072.

McConnell S, Kolopack P, Davis AM. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC): A review of its utility and measurement properties. Arthritis Rheum. 2001;45(5):453-461. https://

onlinelibrary.wiley.com/doi/epdf/10.1002/1529-0131%28200110%2945%3A5%3C453%3A%3AAID-ART365%3E3.0.CO%3B2-W

NCT02006147. Phase I/II Trial of TLC399 (ProDex) in Patients with Macular Edema Due to Retinal Vein Occlusion (RVO). https://clinicaltrials.gov/ct2/show/NCT02006147?term=TLC399&draw=2&rank=2

NCT02803307. A Randomized, Open-label, Parallel, Phase I/II Single-Dose Administration Trial of TLC599 in Subjects with Osteoarthritis of the Knee. https://clinicaltrials.gov/ct2/show/record/NCT02803307?term=TLC599&draw=2&rank=2

NCT02925000. A Phase I/IIa, Open Label, Dose-escalation Study Investigating the Safety, Tolerability, and Pharmacokinetics of Intravenous Liposomal Vinorelbine Tartrate Injection in Patients with Advanced Malignancy. https://clinicaltrials.gov/ct2/show/NCT02925000?term=TLC178&draw=2&rank=1

NCT03005873. A Phase IIa, Randomized, Double Blinded, Placebo Controlled, Dose Finding Study for Single Dose Administration of TLC599 in Patients with Osteoarthritis (OA) of Knee. https://clinicaltrials.gov/ct2/show/record/NCT03005873?term=TLC599&draw=2&rank=4

NCT03093701. TLC399 (ProDex) in Subjects with Macular Edema Due to Retinal Vein Occlusion (RVO). https://clinicaltrials.gov/ct2/show/NCT03093701?term=TLC399&draw=2&rank=1

NCT03591146. A Phase I/II, Randomized, Double-blind, Comparator-controlled, Dose-escalation Study to Evaluate the Safety, Pharmacokinetics, and Efficacy of TLC590 for Postsurgical Pain Management Following Inguinal Hernia Repair. https://clinicaltrials.gov/ct2/show/NCT03591146?term=TLC590&draw=2&rank=1

NCT03754049. A Phase 2, Open-label, Pharmacokinetic Study of a Single Intra-articular Administration of TLC599 in Subjects with Mild to Moderate Osteoarthritis of the Knee. https://clinicaltrials.gov/ct2/show/NCT03754049?term=TLC599&draw=2&rank=1

NCT03838133. A Phase 2, Randomized, Double-blind, Comparator- and Placebo-controlled Study to Evaluate the Safety, Pharmacokinetics, and Efficacy of TLC590 for Postsurgical Pain Management Following Bunionectomy. https://clinicaltrials.gov/ct2/show/NCT03838133?term=TLC590&draw=2&rank=2

NCT04123561. A Phase 3, Randomized, Double-blind, Placebo- and Active-controlled Study to Evaluate the Efficacy and Safety of TLC599 in Patients with Osteoarthritis of the Knee. https://clinicaltrials.gov/ct2/show/NCT04123561?term=TLC599&draw=2&rank=3

Pham T, van der Heijde D, Altman RD, Anderson JJ, Bellamy N, Hochberg M, Simon L, Strand V, Woodworth T, Dougados M. OMERACT-OARSI initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited. Osteoarthritis Cartilage. 2004;12(5):389-399. https://www.oarsijournal.com/article/S1063-4584(04)00025-1/pdf

Roos EM, Klassbo M, Lohmander LS. WOMAC osteoarthritis index. Reliability, validity, and responsiveness in patients with arthroscopically assessed osteoarthritis. Western Ontario and MacMaster Universities. Scand J Rheumatol. 1999;28(4):210-215.

Scanzello CR, Goldring SR. The role of synovitis in osteoarthritis pathogenesis. Bone. 2012;51:249-257. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3372675/pdf/nihms-360129.pdf

Spector TD, MacGregor AJ. Risk factors for osteoarthritis: Genetics. Osteoarthr Cartil. 2004;12(Suppl. A):S39-S44.
Sophie R, Hafiz G, Scott AW, Zimmer-Galler I, Nguyen QD, Ying H, Do DV, Solomon S, Sodhi A, Gehlbach P, Duh E, Baranano D, Campochiaro PA. Long-term outcomes in ranibizumab-treated patients with retinal vein occlusion; the role of progression of retinal nonperfusion. Am J Ophthalmol. 2013;156(4):693-705. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4030598/pdf/nihms577443.pdf

TLC Press Release. EMA Grants Orphan Drug Designation to TLC178 for the Treatment of Soft Tissue Sarcoma. January 22, 2019. https://www.tlcbio.com/en-global/press-releases/detail/News_20190122

TLC Press Release. TLC Announces First Patient Enrollment in EXCELLENCE Trial Evaluating Single and Repeat Administrations of TLC599. November 27, 2019. https://www.tlcbio.com/en-global/press-releases/detail/News_20191127

TLC Press Release. TLC Announces Initiation of Phase III Pivotal Clinical Trial of TLC599 for the Treatment of Osteoarthritis Knee Pain. October 01, 2019. https://www.tlcbio.com/en-global/press-releases/detail/News_20191001

TLC Press Release. TLC Announces Part 1 Analysis of TLC590 Phase II Clinical Trial for Postsurgical Pain Management following Bunionectomy. June 14, 2019. https://www.tlcbio.com/en-global/press-releases/detail/News_20190614

TLC Press Release. TLC Announces Positive End-of-Phase II Meeting with FDA for TLC599 in Knee Osteoarthritis. April 15, 2019. https://www.tlcbio.com/en-global/press-releases/detail/News_20190415

Wang YX, Zhang JS, You QS, Xu L, Jonas J. B. Ocular diseases and 10-year mortality: The Beijing Eye Study 2001/2011. Acta Ophthalmologica. 2014;92(6):e424-e428.

Warfield CA, Kahn CH. Acute pain management. Programs in U.S. hospitals and experiences and attitudes among U.S. adults. Anesthesiology. 1995;83(5):1090-1094.

Yeh G. TLC Corporate Presentation. http://ir.tlcbio.com/static-files/b5b80555-99c9-45c7-8ff7-592027767f12
Zhang W, Nuki G, Moskowitz RW, Abramson S, Altman RD, Arden NK, Bierma-Zeinstra S, Brandt KD, Croft P, Doherty M, Dougados M, Hochberg M, Hunter DJ, Kwoh K, Lohmander LS, Tugwell P. OARSI recommendations for the management of hip and knee osteoarthritis: Part III: Changes in evidence following systematic cumulative update of research published through January 2009. Osteoarthritis Cartilage. 2010;18:476-499. https://www.oarsijournal.com/article/S1063-4584(10)00046-4/pdf

DISCLOSURE

Never invest in any stock featured herein unless you can afford to lose your entire investment.

Neither Encode Ideas LP, nor its employees and affiliates are registered as investment advisors or broker/dealers in any jurisdiction whatsoever. The information contained herein is based on sources that Encode Ideas LP believes to be reliable but is not guaranteed by us as being accurate and does not purport to be a complete statement or summary of the available data. Readers should always do their own due diligence and consult a financial professional. Encode Ideas LP encourages readers and investors to supplement the information in this report with independent research and other professional advice. All information on the featured company is provided by the company profiled, or is available from public sources and Encode Ideas LP makes no representations, warranties or guarantees as to the accuracy or completeness of the disclosure by the profiled company. Any opinions expressed in this report are statements of judgment as of the date of publication and are subject to change without further notice, and may not necessarily be reprinted in future publications or elsewhere.

None of the materials or advertisements herein constitute offers or solicitations to purchase or sell securities of the company profiled herein and any decision to invest in any such company or other financial decisions should not be made based upon the information provide herein. Instead, Encode Ideas LP strongly urges you conduct a complete and independent investigation of the respective companies and consideration of all pertinent risks. Encode Ideas LP does not offer such advice or analysis, and Encode Ideas LP further urges you to consult your own independent tax, business, financial and investment advisors. Investing in micro-cap and growth securities is highly speculative and carries and extremely high degree of risk. It is possible that an investor's investment may be lost or impaired due to the speculative nature of the company profiled. Encode Ideas LP. its operators, owners, employees, and affiliates may have interests or positions in equity securities of the companies profiled on this website, some or all of which may have been acquired prior to the dissemination of this report, and may increase or decrease these positions at any time.

This report may contain forward-looking statements, which involve risks and uncertainties. Accordingly, no assurance can be given that the actual events and results will not be materially different than the anticipated results described in the forward-looking statement. There are a number of important factors that could cause actual results to differ materially from those expressed in any forward-looking statements made by Encode Ideas LP about the company profiled. These factors include that company's success in their business and operations; the activities of new or existing competitors, the ability to attract and retain employees and strategic partners, the ability to leverage intangible assets, the ability to complete new projects at planned costs and on planned schedules and adoption of the Internet as a medium of commerce, communications and learning. If applicable, investors are also directed to consider other risks and uncertainties discussed in documents filed by the profiled company with the Securities and Exchange Commission. Encode Ideas LP undertakes no obligation to publicly release the result of any revisions to these forward-looking statements, which may be made to reflect events or circumstances after the date hereof or to reflect the occurrence of unanticipated events.

In no event shall Encode Ideas LP, its operators, owners, employees, and affiliates be liable (jointly or severally) for any special, incidental, indirect or consequential damages of any kind, or any damages whatsoever resulting from loss of use, data or profits, whether or not advised of the possibility of damage, and on any theory of liability, arising out of or in connection with this report. If any applicable authority holds any portion of this section to be unenforceable, then liability will be limited to the fullest possible extent permitted by applicable law.

Encode Ideas, LP is engaged with TLC to provide investor awareness and research coverage. Please visit our website for full disclosure.

Following publication of any report or update note, Encode Ideas, LP intends to continue transacting in the securities covered therein, and we may be long, short, or neutral thereafter regardless of our initial recommendation.